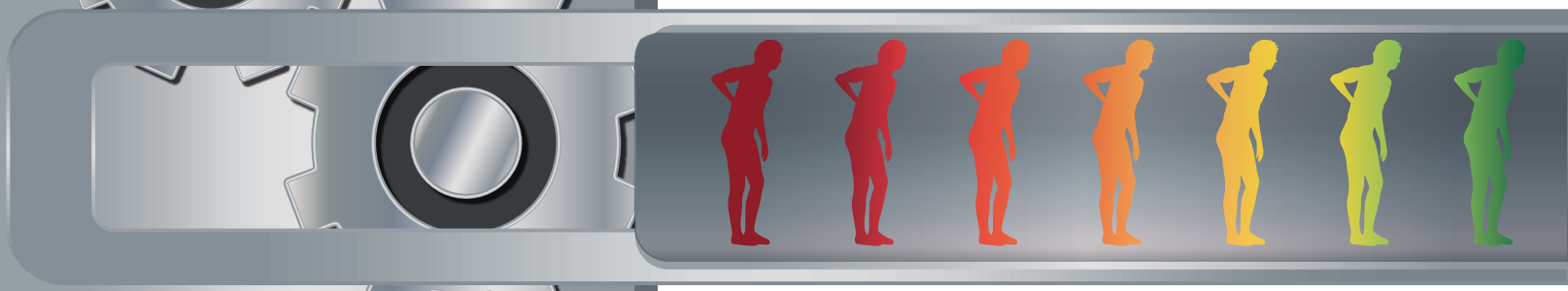
HARMS PROGRAM MANUAL

A System to Support Routine Urine Drug Testing in a Primary Care Setting

1st Edition



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HARMS Program Manual Introduction

This section introduces the HARMS Program as a system to make urine drug testing (UDT) practical in your clinical setting. Whether you are already systematically applying UDT in your patients prescribed opioids for chronic pain, or are simply considering it, this is an overview to help you plan and refine your course. The waters of UDT are at-times cloudy, and we are hopeful others can learn from our successes and failures.

April 30, 2020

Welcome to the HARMS Program Manual! This manual is the culmination of 5+ years of work designing, implementing, studying and refining a clinic-wide system to make urine drug testing (UDT) practical in primary care. Although developed for use in patients with chronic pain prescribed opioids, many of the same UDT principles can be applied to patients prescribed opioids to treat opioid addiction (opioid agonist therapy such as methadone or buprenorphine/naloxone). We hope others will be able to learn from our successes and initial failures as they consider incorporating regular UDT into their clinical practice. As frontline clinicians practicing in a resource-limited setting, we are confident that the innovations developed here offer a practical approach that can be replicated in other clinical settings. We are hopeful they can be applied to lessen the suffering of patients suffering with chronic pain, addiction, and the many people lying on that grey area in between.

It is critical to highlight that the goal of urine drug testing is *not* to "catch" patients or to punish them. The most important thing to remember from this manual is that the goal of urine drug testing is simply to inform the risk/benefit balance for a given patient when prescribing opioids. This overriding principle guides the answers to questions about what to do if a patient does not provide a UDT; has an expected result; has an aberrant result that is anywhere from mild to major, a single concern or repeated concerns; and the innumerable other questions that may arise as you start applying UDT. *The clinical Gestalt is critical, and UDT simply informs that clinical Gestalt*. With the informed clinical Gestalt, open discussions conducted in a non-judgemental and non-punitive manner can be facilitated with the patient.

For the sake of completeness, let us start with describing why and how the HARMS Program came to be. As frontline family physicians, we were all too aware of the near-impossible task assigned to us for patients suffering with chronic pain - we are expected to manage their chronic pain effectively (with opioids being one of the limited tools in our toolbox), while not causing or enabling opioid addiction or misuse (two of the known risks of these medications). While every clinical decision comes down to balancing the risks and benefits, what makes opioids in chronic pain particularly challenging is that this risk/benefit assessment is inherently limited. Pain is a significant part of the assessment, and because there is no objective test for pain, we are reliant on self-reports. People who are being harmed by these medications (addiction and/or other misuse) happen to be exactly the people who often don't want us to stop prescribing them. For example, if a patient prescribed opioids for chronic non-cancer pain (CNCP) is addicted he may be unwilling to disclose incriminating information for fear of having his prescription stopped and/or even being discharged from one's practice. If someone is selling his opioid medications or trading them for other drugs then he too is inclined to want the opioid prescription to continue. There are few places in clinical medicine where the goals of the patient are potentially so harmful, and so discordant with the goals of the prescribing physician. This is not to say that the patient's self-reported pain is not helpful, only that it does have significant limitations. This limitation necessitates the inclusion of other variables in our risk/benefit analysis of opioids, so that our management and monitoring are as informed and objective as possible.

While we will never have a perfect assessment of potential risks and benefits with opioids in CNCP, UDT offers on objective marker of risk that contributes to a more informed risk/benefit analysis. Patients with substance use disorders are at higher risk for opioid addiction, overdose and death (Busse 2017).

UDT is a central component of safe prescribing with opioid agonist treatment for opioid use disorder (methadone, or buprenorphine/naloxone). Essentially, UDT is a *marker* of clinical stability that is used to inform the risk/benefit balance of prescribing take-home doses. If someone prescribed methadone for example is actively using non-prescribed opioids, or cocaine, this suggests less clinical stability than an otherwise similar person (social status, mental health comorbidities, etc.) who is *not* using these drugs. That patient demonstrating clinical instability may then have take-home doses reduced and/or urine drug testing frequency increased.

Given that UDT informs risk/benefit balance when prescribing opioids to *treat* addiction, we might ask why it can't also be used to inform the risk/benefit balance for patients prescribed opioids for *CNCP*? If someone with CNCP has a concerning UDT result, then does this too not tilt the risk/benefit balance and change if and how opioids are prescribed and further monitored? Numerous guidelines recommend UDT in patients with CNCP prescribed opioids (Gourlay 2005, Katz 2003, Dowell 2016), given its capacity to improve the way opioids are prescribed and/or further monitored for CNCP. However, it has not been widely adopted (Boulanger 2007, Bhamb 2006, Adams 2001). There are numerous reasons for UDT not being widely and effectively implemented into frontline clinical medicine for CNCP (Bair 2010, Kirsh 2015, Reisfield 2007, Starrels 2012).

Prior to starting what would become the HARMS Program, we were well aware of these barriers through our own clinical experience. While we had numerous case examples where we conducted UDT and it drastically changed our understanding of a patient's risk/benefit balance and subsequent management - it was being applied sporadically, heterogeneously and with numerous obstacles. We didn't know who to subject to UDT and how often, nor did we have a way of keeping track of who has been doing his/her required UDT and who hasn't. We didn't know where to conduct the UDT (clinic or lab); which type of UDT to use (immunoassay and/or confirmatory testing with liquid chromatography-mass spectrometry); or how to act on the spectrum of results (minor aberrancy to major, no-shows, etc.). We also had early experiences in which we misinterpreted UDT results, and subsequently had uninformed discussions with patients. We were not surprised to learn that encountering all of these barriers was not unique to our clinic - in fact they're well-documented in the literature. We were also not the first to consider *building a system* to support routine UDT - "Healthcare systems and individual practices will need to be redesigned to support routine UDT" (Bair and Krebs 2010). However, as far we are aware, we are the first to initiate actually building a complete system to support routine UDT.

Over the ensuing years, numerous innovations were developed to address these UDT barriers, in what would collectively become a system known as the HARMS Program (High-yield Approach to Risk Mitigation and Safety). Given that HARMS was built in rural northern Ontario - where human and financial resources are limited - it has the potential to be easily expanded to other clinical settings.

Before giving an overview of how this UDT system (HARMS) works, it is important to acknowledge some UDT caveats. As mentioned, unfortunately UDT has occasionally taken on a punitive quality. That is comp-

letely against the intent of the HARMS Program. The HARMS Program aims to use UDT systematically to inform the risk/benefit balance of opioids, and if risks exceed benefits then the patient is supported while management is modified. Stopping the opioid prescription (even with an appropriately slow taper), ***without supporting the person***, can prove detrimental to the patient and must be avoided. UDT is simply a tool to inform our risk/benefit balance when deciding about if and how to prescribe these medications. UDT informs the clinical picture but is not meant to be a replacement for good clinical judgement. There are many other factors that contribute to the risk/benefit balance and these need to be included in treatment decisions. In addition, especially with point-of-care (immunoassay) testing, there exists the possibility of false positives and negatives. It is important to know the limitations of testing prior to discussing with the patient and acting on results. The START-IT Tool *(see Chapter 7)* is a helpful way of attaining clinically meaningful feedback for any given IA result, including test limitations (false positives/negatives, etc.) and customized explanations. If you're still not sure about what a result means, consider asking an expert in the area. The clinical biochemist at the lab can be very helpful for explaining the meaning and limitations of confirmatory testing (LC-MS). Even after applying UDT for >5 years now, we still have questions that arise and always find the clinical biochemist helpful.

The HARMS Program (UDT System) is applied to all patients prescribed opioids for CNCP at our clinic with few exceptions - *see Chapter 1*. Once a patient is identified as being prescribed opioids for CNCP, the next step upon entering HARMS is estimation of risk, which will then guide how the UDT system is applied. The physician then notifies the clinical administrator (a designated, non-medical member of the clinic staff such as a secretary) of risk estimate, and the patient is added to a master list. Administration then randomly selects patients off of that master list at a rate concordant with risk - higher risk patients are subjected to more frequent UDT than lower risk patients. Once selected, the patient is called and booked for a UDT at the clinic. At our clinic, the UDT is conducted with a clinical employee who has no formal medical training. This was done to preserve precious nursing resources. The START-IT tool is applied at the UDT appointment to simplify the whole process of conducting a UDT on-site. START-IT utilizes a tablet PC to collect all of the information required for the test, including the immunoassay ("point-of-care") UDT result. The START-IT interpretation is then uploaded into the electronic medical record (EMR) with the click of a button. If the result is unexpected, then the physician is notified of the result immediately. As applicable, the sample is then sent to the lab for confirmatory testing. If a patient is not providing a UDT despite repeated attempts, then the physician is notified of this as well. With the UDT results (or lack thereof) and any other new piece of information informing the clinical Gestalt, the physician can then consider altering prescribing and monitoring strategies accordingly. If risk level is changed or opioids are tapered and stopped, administration is notified and updates the master list.

The process is iterative, with each pass through the system providing more information about a given patient. If concerns are identified, then monitoring is tightened to hone in on the most accurate assessment we can get of substance use and risk/benefit balance.

To summarize the main innovations of HARMS and how they address previous UDT barriers:

- A clinic-wide system was built to standardize the approach for patients and prescribers *Figure 1, Page viii (System Overview infographic)* . Given that all patients have some risk, the system applies "universal precautions" to all patients with CNCP prescribed opioids (with a few exceptions).
- The HARMS Program is carried out almost completely by clinical administration *Figure 2, Page ix (Process for systematic UDT infographic)* . This was done to offload the workload as much as possible from busy physicians.

- The *HARMS Risk Ladder* *Figure 3, Page x (Risk Ladder infographic)* as created to be an intuitive and versatile approach for not only determining how often to conduct UDT for a given risk level, but also how to adapt to the full spectrum of results (from minor concern to major). It takes principles for risk mitigation and safety used in opioid agonist treatment for addiction, and applies them to opioid-prescribing in CNCP.
- START-IT *Figure 4, Page xi (Start-IT infographic)* is a one-stop shop for UDT in the office, as mentioned above. It collects all of the required information for a UDT and interprets it within the limitations of the test. The report is uploaded into the EMR with the click of a button. This is an important step in both reducing workload, and more important ensuring accuracy in the interpretation of UDT results. The literature has shown that physicians are not adept at interpretation of UDT and can even make disastrous mismanagement decisions based on these erroneous interpretations (Reisfield 2007, Starrels 2012, Christo 2011). Automated interpretation helps address this barrier.

All of this is well and good, but does such a system actually work? We conducted a retrospective chart review of all patients in our program who were not already identified as high-risk, and followed them for a 12-month period. What we found was that 19% (15/77) of patients had UDT results that directly changed management (starting opioid agonist treatment for addiction, escalation to a high-risk stream, or in a minority of cases tapering and discontinuing opioid medication) (Shahi and Patchett-Marble, Journal of Opioid Management 2020).

Since that study, numerous modifications have been made including the creation of more risk categories; changing the method of randomization from 10% per month for low risk patients to 1-2 tests per year; creation of a "recall list"; upgrades to START-IT including analyzing more panels and giving more customized information about what results mean and when to send for confirmatory testing. Now that HARMS has been created, studied, and refined it is ready for clinical expansion and more rigorous evaluation. Recent efforts have been focused on packaging for clinical dissemination with the creation of professional infographics, a website, a smartphone app and this manual.

If you are interested in participating in the evaluation of HARMS through becoming a pilot site, then please let us know. START-IT has been built to easily collect data (in addition to its other roles making UDT practical in the office).

As you review this manual and apply UDT to real-life patients, we would like to stress one more time that the intent is to inform the risk/benefit balance of opioids and guide if and how they should be prescribed and monitored. It is not the only marker. It is intended to complement the rest of the clinical Gestalt. This is the first edition of this manual and will continue to evolve in the next five years as it has over the last five. We appreciate you taking the time and energy to explore our system for urine drug testing,

Sincerely,

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HARMS Program Founder and Lead
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Website: www.harmsprogram.ca

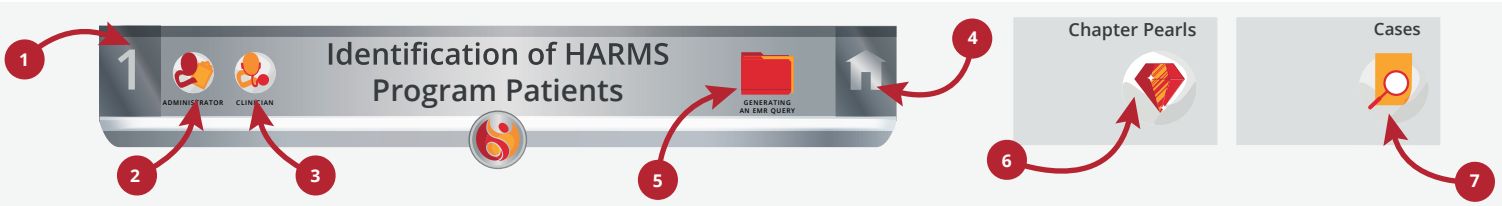
Case 1

You are a family physician with a full-scope of practice that includes chronic pain. You have dozens of patients in your practice that are prescribed opioids for chronic pain, and you feel uncomfortable about a number of them but can't put your finger on why. Most of these patients you inherited from another physician who was quite liberal with the use of opioids in the CNCP population. You have done no regular monitoring in this population previously. You are interested in sorting out who might be benefitting with these medications and who might be harmed, so that you can adjust their treatment accordingly, but don't know where to start. You consider validated patient questionnaires (ORT, SOAPP-R, DIRE, DAST, etc) to assess for general risk and addiction but don't have time and have heard they're not overly effective ("patients can lie"). On several occasions you have been very concerned about a patient and ordered a urine drug test, which provided concerning results and changed management, but it was a logistical hassle and you have no idea how you would apply this across your practice. What can you do to get started?

If this sounds like you, then you are in the right place! We are hopeful this manual can be helpful to you and act as a guide to applying a UDT system at any stage - from your initial consideration, to clinical implementation, to subsequent refinements unique to your own setting.

How to Use this Manual

This manual is meant to be a reference for questions you may encounter when conducting routine UDT for patients prescribed opioids for CNCP. It is intended to have sections to guide clinicians, as well as sections to guide clinical administrators in their critical role of coordinating the program. The following section will assist in navigating the manual.



1	1, 2, 3 etc.	Chapter Number, click to return to first page of the chapter
2		Relevant to clinician
3		Relevant to administrator
4		Return to the table of contents
5		Supplemental resources (pdfs, handouts, websites and other documents)
6		Pearls or key points
7		Cases are meant to illustrate pearls, therefore they are short and to the point. For example, instead of telling you all of the medications the patient is on, it will just list the relevant ones. Also, cases may not be realistic in the sense that we will list just a long-acting opioid without mention of a short-acting opioid, when in reality most patients on long-acting opioids are also on breakthrough short-acting opioids. This is done for simplicity and to focus on key points instead of unnecessarily long cases. It is assumed that you have done a history, physical, and looked at other pain control options, etc. This manual is focused on UDT and its application to safety assessments.

Figure 1: Overview of HARMS program

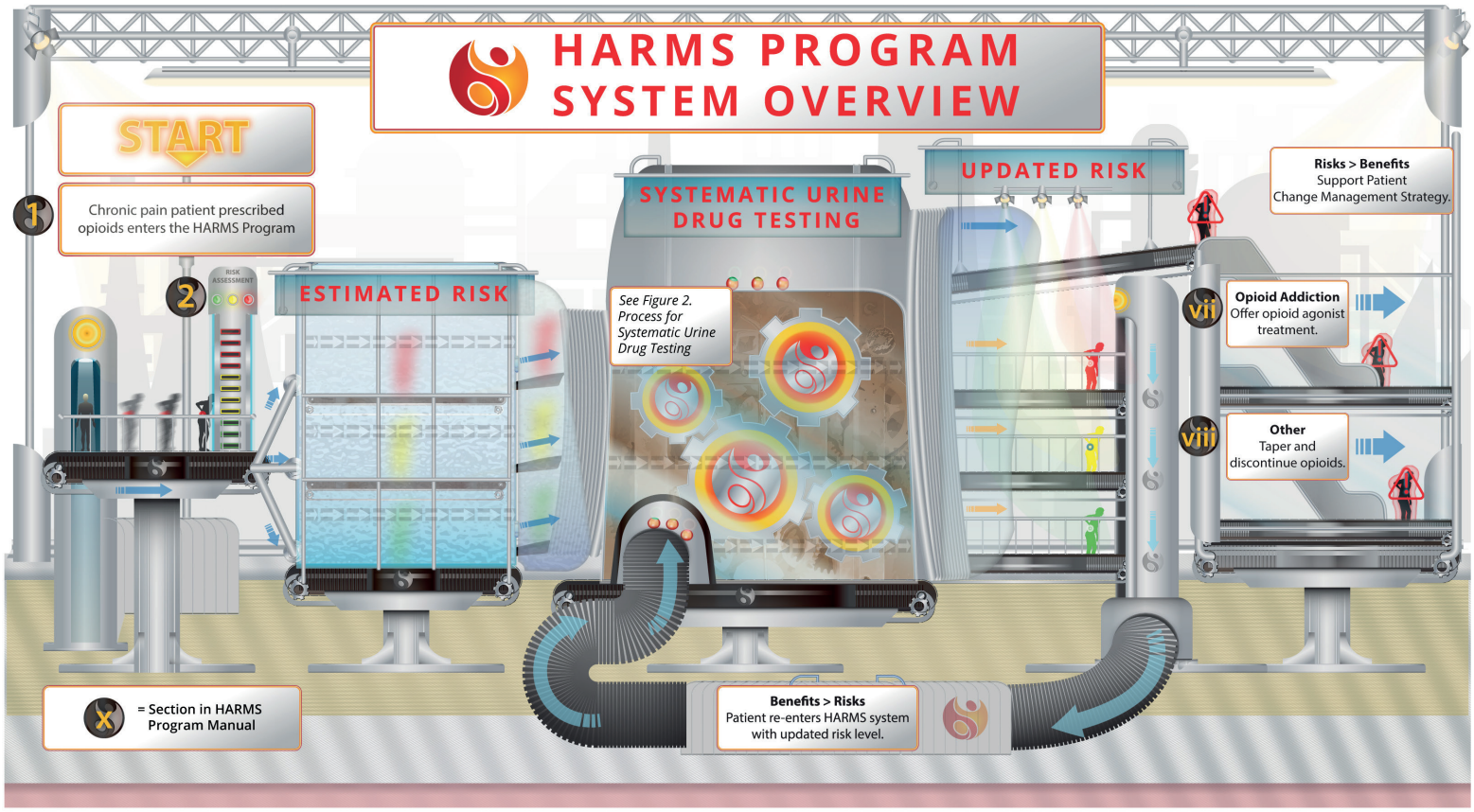


Figure 1. Illustrated here is an overview of the HARMS Program. Patients prescribed opioids for chronic non-cancer pain have their initial risk estimated based on any combination of validated risk stratification tool(s), past medical history, previous UDT results, behavioural observations, or simply the clinical Gestalt if physician time is a limiting factor for formalized stratification. The patient enters the UDT system (See Figure 2) with a risk estimate along a spectrum from low to high and UDT is conducted at a frequency concordant with that risk. As new information (from UDT or otherwise) tilts the risk/benefit balance, the risk is updated accordingly. If benefits still outweigh risks, then the patient re-enters the process using the updated risk level for the next iteration. Conversely, if it is found that risks outweigh benefits then the patient would be supported while management is changed. If opioids are no longer prescribed for chronic pain then that patient would exit the HARMS Program. It is critical when applying UDT to recognize that the intent is not to punish patients, but to inform the risk/benefit balance and guide subsequent patient discussion and management decisions.

Figure 2: The HARMS UDT System

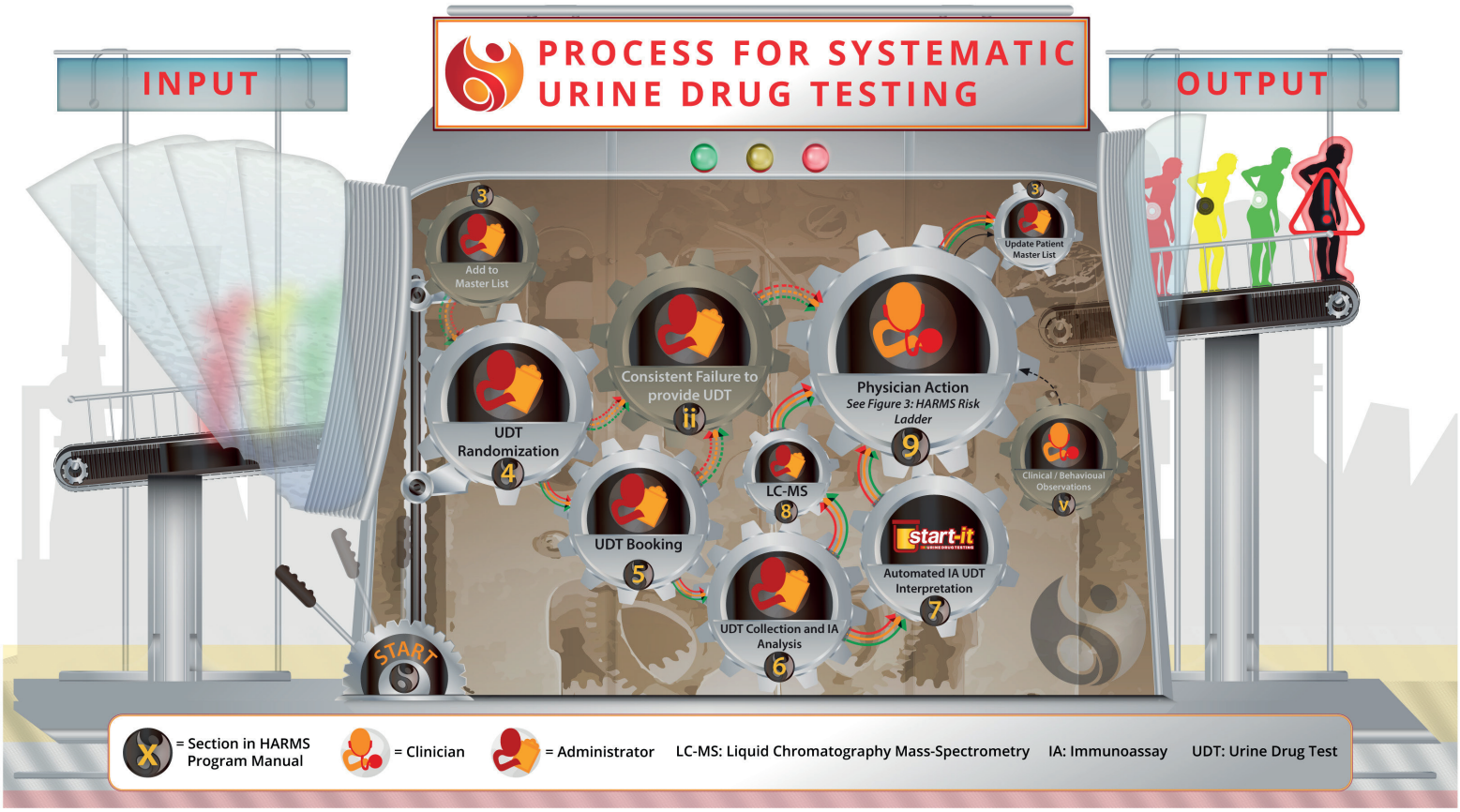


Figure 2. The HARMS UDT system effectively refines the estimate of risk/benefit balance with each iteration of the process. The process, as demonstrated here, was structured so that most of the cogs in the system would fall under the responsibility of clinical administrators. This offloads responsibility, where possible, from busy clinicians. When a patient enters HARMS for the first time, the name and risk category are added to a HARMS Patient Master List. Patients are then randomly selected from that list for UDT at a rate concordant with risk. Once selected, the patient is then notified of a UDT appointment at the clinic in the next 36 hours. UDT is then collected and analyzed using immunoassay (IA). START-IT automatically interprets the results within the limitations of the test. The physician is then notified of the UDT IA result and interpretation, while awaiting confirmatory testing results as applicable. If the patient is rand-omized and does not provide a UDT for whatever reason (unable to contact, no-show, cancellation, unable to urinate, etc.), then the patient stays on a "recall list" until the UDT is provided. If despite repeated attempts, the patient continues to not provide a sample, then the physician is notified by clinical administration. The information from the UDT process (results themselves, or a failure to provide UDT) is then used as the physician considers taking action. The HARMS Patient Master List is then updated with any changes to the risk level. If the opioid prescription is continued for chronic pain then the patient will re-enter the cycle with the updated risk level.

Figure 3: The Risk Ladder

Figure 3. The Risk Ladder guides not only how to tailor prescribing and monitoring to a patient's estimated risk, but it also advises how to move on the ladder in response to any situation. The initial risk estimate guides the starting place on the Risk Ladder, with subsequent movement on the ladder being informed by new information: UDT results, behavioural observations, mental health issues, changes in social stability, and any other new piece of information that informs the risk/benefit balance. The movement on the ladder is in direct proportion to the degree of concern. A significant concern (from UDT or otherwise) means significant movement up the ladder (as indicated by the red arrows). If opioid addiction is identified, then the patient moves to the top rung and opioid agonist treatment for addiction should be considered. Similarly, if the risks are greater than the benefits but there is no opioid addiction identified, then the patient moves off the ladder as support is given and management is changed. If the patient demonstrates clinical stability that lowers apparent risk and/or increases benefits, then he/she can move down the ladder (as indicated by the green arrows).

Figure 4: START-IT

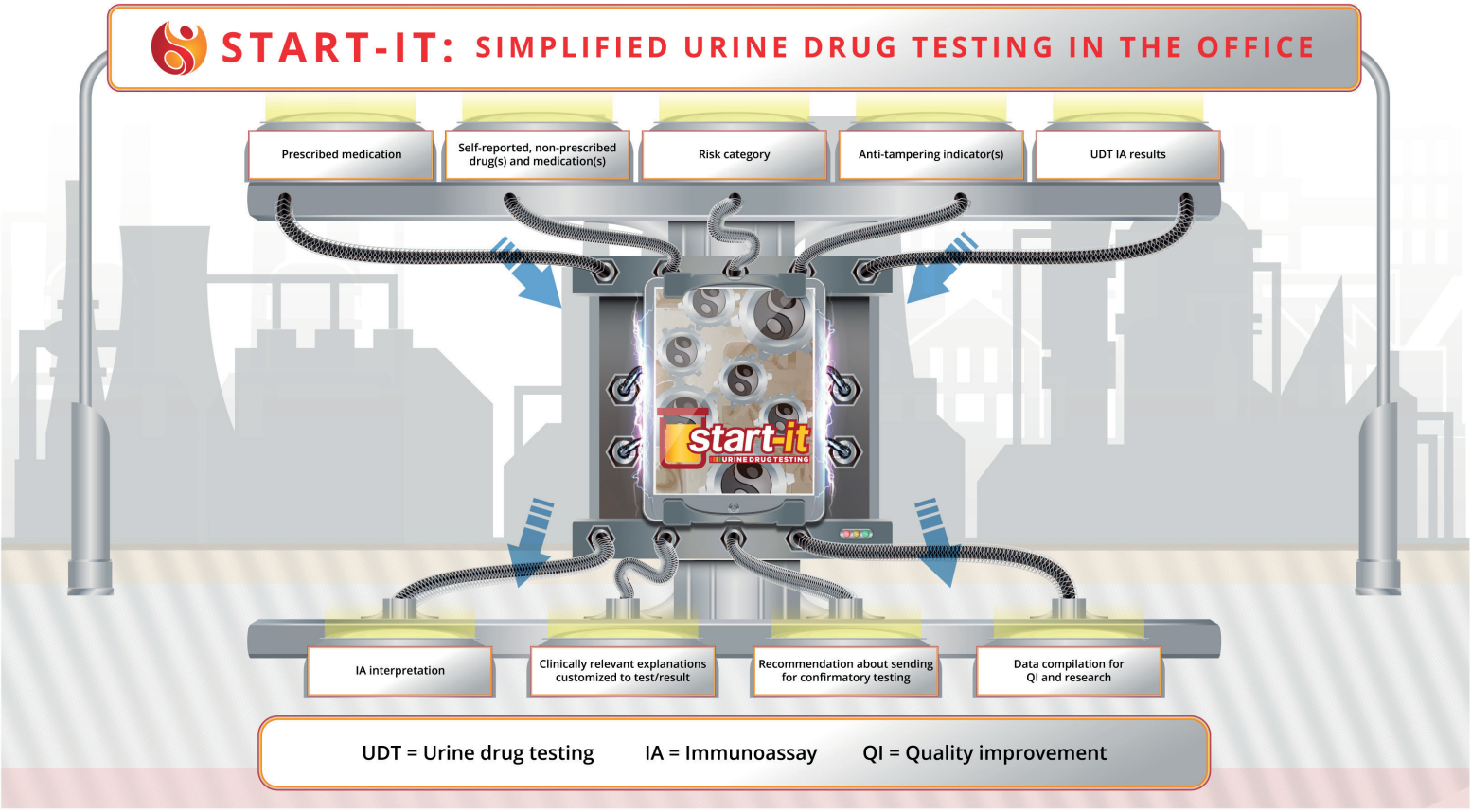


Figure 4. START-IT was designed to simplify the process of UDT in the office. It uses a tablet PC to collect the required information for a UDT, and then interprets that information within the limitations of the test. START-IT provides a customized, pragmatic report indicating exactly what this result may mean for this specific patient, as well as additional considerations for the clinician given the inherent limitations of UDT. The report is synchronized with the electronic medical record (EMR) with the click of a button. START-IT also tracks data which can be used for quality improvement and research purposes. The automation of START-IT ensures that no medical personnel are required for the administration of urine drug testing, IA interpretation, or even in making the decision to send for confirmatory testing with LC-MS. This is an important part of the HARMS Program in that it makes UDT less burdensome for physicians and therefore more practical in frontline medicine.

Disclaimer

The HARMS Program, START-IT and this manual were developed in Marathon, ON and have been used clinically at the Marathon Family Health Team. All information contained herein is intended for use by qualified clinicians and as educational tools to assist in fair and practical interpretation of urine drug testing results. Further, UDT should be seen as a way of making opioid prescribing more informed and is not intended for punitive action against any patient. Clinical judgement is important, and thus this is not meant to be followed blindly. Final analysis and recommendations must be evaluated for each individual patient and use of the information for final patient care decisions must be carefully weighed by the treating clinician and should be discussed with the patient before implementing medication or therapeutic changes. If you are unsure we highly recommend consulting your local clinical biochemist or a specialist in the area.

The HARMS Program addresses one aspect of opioid management for chronic non-cancer pain (the UDT com-ponent for monitoring safety). HARMS does not attempt to standardize and systematize the other important components (history and physical, non-opioid management, etc.) This manual is not meant to imply that these other facets are un-important, only that they are more difficult to work into a clinic-wide program with various practice styles, time availability, etc. HARMS intentionally addresses one aspect of prescribing opioids for chronic pain (UDT) and aims to do it effectively and efficiently.

The authors of this manual have done their best to incorporate best-evidence into this program. The authors of HARMS/START-IT and this manual cannot guarantee their accuracy or completeness and the information obtained by the use of these is not a substitute for clinical judgement. The authors take no responsibility for the actions you take based on this manual - clinical judgement and evaluation in your specific clinical setting, and incorporating specific patient scenarios, supersede any general recommendations given here. Clinical application of the information obtained by use of any part of this manual, or any of the tools described herein, is the sole responsibility of the user.

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Identification of HARMS Program Patients

Now that we've covered why a system for UDT might be important, let's look at the first step in applying it - identification of eligible patients...

One of the challenges when we first started designing a program to apply UDT in CNCP was in deciding who should be enrolled. Unfortunately, the literature supports that our behavioural observations are not enough to identify who is at risk for being harmed by these medications.[1,2] As a result, it was decided to apply "universal precautions" to everyone. This is consistent with more recent "expert recommendations".[3] Everyone at our clinic prescribed opioids long-term for CNCP is part of HARMS and is randomized to provide UDT, with a few exceptions.

There is a spectrum between those who use opioids one week per year for a pain flare, and those who take multiple doses every day. Should these patients be monitored in the same manner? While a cutoff using average morphine equivalent dose per day would be a reasonable way to separate who is enrolled in HARMS and who isn't, it was felt that having physicians calculate this could present unnecessary impediments to physician buy-in. As a result, it was decided to use as a general cut-off "average daily use". Meaning if the person gets, for example, an average of 30 tablets of Tylenol #3 per month he would be enrolled. The second point of clarification is around what qualifies as "chronic pain". We stuck with the definition used by CDC and others that it is pain lasting >90 days or past the time of normal healing.[4] To summarize:

Inclusion:
Averaging daily use of opioid (i.e. averaging ≥1 dose/day, or fentanyl patch, etc.)
Chronic pain lasting >90 days or past the time of normal healing

Exclusion:
Palliative and/or cancer pain
Significant mobility issues (i.e. cannot leave house)
Dispensed in a nursing home/supervised setting

When starting the HARMS Program, practically speaking, how might one go about finding all the patients that meet these criteria? What we did, and what we would recommend to others depending on your EMR capacity, is to have clinical administration run a query that generates a patient list. The Association of Family Health Teams of Ontario (AFHTO) has created resources to help guide this, including a pdf EMR Query for HARMS Patient Identification from AFHTO and a website https://www.afhto.ca/news-events/news/getting-started-opioid-use-registry.

The list generated from the query has all patients prescribed opioids, but does not differentiate acute from chronic pain, nor does it identify palliative/cancer pain. At our clinic, we gave each physician this list of his/her patients prescribed an opioid in the last 12 months. The physician then reviews his/her list and removes patients that don't qualify (in our case, the majority of patients excluded were because they were prescribed opioids for acute pain). If desired, the physician may even assign risk categories at the same time on this same list (see Ch. 2 – Initial Risk Stratification), and hand back to clinical administration who will formulate the master list (see Ch. 3 – Patient Master Lists – Creation and Maintenance). Patients are then randomized from this master list (see Ch. 4 – UDT Selection). We recommend this approach of applying risk categories at the time of enrollment - using the clinical Gestalt to dictate risk category - as it consumes significantly less time than the alternative of applying formal risk stratification tools and/or baseline UDT prior to assigning a risk category. However, if time and energy allow, you may consider using these. While not in clinical use at the time of this 1st edition of the HARMS Manual, a future version of START-IT may also allow automated application of validated risk stratification tool(s).

For patients identified using the query who are "unattached" (i.e. do not have a family physician or Most Responsible Physician - MRP), it is still important to review their eligibility for HARMS. A non-physician staff member may feel comfortable checking this list to see if opioids are prescribed long-term, averaging daily use, and patient has a non-palliative/non-cancer diagnosis. Most patients will once again be excluded because opioids were for acute pain. For patients not immediately excludable, physician consultation may be required. At our clinic, once the list of

unattached patients prescribed an opioid was reviewed, we didn't have any patients prescribed opioids for chronic pain without an MRP.

Additional Resources:

1) AFHTO EMR Query Online Link
(https://www.afhto.ca/news-events/news/getting-started-opioid-use-registry)

2) AFHTO EMR Query pdf for HARMS Patient Identification
(EMR Query for HARMS Patient Identification from AFHTO.pdf)

Cases

Case 1

Mr. Smith is on your opioid list generated by the EMR query. You know that for his chronic shoulder pain he is prescribed oxycodone/acetaminophen (Percocet) at 30 tabs/month for the about three years. He is mobile and working. Should he be a part of the HARMS Program?

He should be part of the HARMS Program. Consider assigning a risk category immediately based on your clinical Gestalt (see Ch. 2 for important markers of risk), however if time and energy allow you may consider applying a validated risk stratification tool and/or baseline UDT for guidance.

Case 2

Mr. Thompson is on your opioid list generated by the EMR query. You prescribe hydromorphone 2mg TID prn for the last 2 months for back pain. He has lumbar spine decompression surgery booked next month. Should he be enrolled in HARMS?

In this case, Mr. Thompson would not be a candidate currently for HARMS because he has been prescribed opioids less than 3 months. When considering HARMS enrollment, you may also consider pending interventions and their likelihood for reducing pain (in this case his surgery).

Case 3

Mrs. White is prescribed short-acting morphine 5mg for intermittent back pain flares. You review her file and she received 60 tabs on two occasions over the past year. Should she be enrolled in HARMS?

No, she is averaging less than daily use. Your clinic may consider an alternative cutoff for quantity/frequency, such as using average morphine equivalents/day, however we prioritized simplicity. A recurrent theme with HARMS is that clinical judgement always prevails. If there is a high level of concern about misuse in this patient then you may still consider including in the program.

Chapter Pearls

- Universal precautions are necessary - physicians are unable to identify patients being harmed by opioids based on patient self-reports, or clinical/behavioural observations[1,2,5], therefore objective and universally applied monitoring is needed. No patient is zero risk and therefore UDT should be applied to everyone prescribed opioids for CNCP (with rare exclusions as above).
- Use the EMR query to quickly screen who should be part of the HARMS Program and then physicians can do the final check of inclusion/exclusion criteria.
- Standardization of HARMS was prioritized in its design. As much as possible, HARMS is meant to be easily consistent between different clinics, and different physicians within the same clinic. There are always grey areas and these will be discussed throughout this manual.

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Now that patients prescribed opioids for CNCP have been identified, the next step is to determine individual risk levels that guide how tightly we monitor and prescribe for that person...

Initial Risk Stratification

Now that we've identified eligible patients for HARMS, we need to make an initial estimate of risk to guide how tightly we monitor this patient with urine drug testing (UDT). The key here is that there are a number of different strategies for risk stratification and physicians should take into account the time and energy available when deciding which method(s) to utilize. There is no "one size fits all" method...

Risk stratification plays a very important role in the HARMS Program as it guides how we prescribe and monitor opioid treatment. It is important to remember that this assessment of risk is an estimate based on the information available to us at one point in time, and that this risk estimate is continually evolving as new information arises. In fact, the whole point of UDT is to provide ongoing information to inform this risk estimate. UDT is therefore simply intended to inform risk/benefit balance, however it is not the only factor. This overall risk/benefit balance (including UDT results and other clinical factors) then informs our prescribing and monitoring of opioids (to see how we may adjust risk category as new information arises, see Chapter 9 – Managing UDT Results).

Monitoring with UDT is informing the risk estimate, and the refined risk estimate feeds back to guide frequency of further UDT monitoring. Risk stratification and UDT therefore complement each other through each iteration of the cycle. We must remember that there are potential harms in doing UDT too frequently or too infrequently. More UDT means more inconvenience for the patient (and physician who addresses the results), increased costs to the healthcare system, and in the case of immunoassay UDT - higher risk of false positives or negatives and in the untrained interpreter risk of subsequent management errors. Likewise, less UDT may mean less information about the patient's risk/benefit balance (risks in particular). Naturally, to balance the two variables of convenience and safety we estimate someone's risk and conduct UDT at a rate concordant with that risk estimate. High risk patients get more frequent UDT in the interests of safety, at the expense of some convenience. Low risk patients get less frequent UDT in the interest of convenience, at the possible expense of safety. Each cycle of UDT (and subsequent risk adjustment as applicable) hones in on the best estimate of someone's risk. Prescribing and monitoring strategies, meant to balance safety and convenience, are in essence adapting to the evolving risk estimate.

To summarize the importance of risk stratification, remember that the initial estimate guides where a patient starts on the spectrum of prescribing and monitoring, from tight to loose. But the iterative process of the HARMS Program is also important because it provides ongoing information to refine that risk estimate. We are trying to adapt to a moving target.

Now that the importance and clinical application of risk stratification has been described, let's discuss different options to aid in risk stratification. Think of this list as a menu that you can pick and choose from. Do not feel compelled to use everything if you don't have the capacity to do so. Remember, HARMS is meant to be practical and adaptable for your unique situation/setting. The highest yield indicator of risk is likely your clinical Gestalt.

Behavioural observations: There are numerous behavioural observations that have been reported to indicate an increased risk. See Appendix E for details of behaviours that indicate someone is at increased risk. Remember that while there are observations that may increase someone's risk, an absence of these observations does not show that someone's risk is zero, and that patients that have no behavioural concerns can still have concerns on urine drug testing.[1,2] An absence of behavioural concerns is therefore *not enough* in itself to establish someone's risk.

Medical History: There are numerous indicators of risk on a patient's medical history. Many of these are variably captured using validated risk assessment tools (described further below).

In terms of prescription opioid use disorder, a recent systematic review identified single high-quality studies which demonstrated the following risk factors as being associated with substantial increase in the likelihood of developing a prescription opioid use disorder[3]:

- **History of substance use disorder**[3]
  - History of substance (opioid or nonopioid) or tobacco use (strongly predictive)[4]
    - Alcohol abuse is included as there is evidence in this population of polysubstance abuse[5]

- **History of any pain disorder**[3]

- **Mental health diagnosis** such as personality disorder, somatoform disorder, psychotic disorder or anxiety disorder[3]
  - Opioids can be used for mood altering properties[6]
  - Having a lifetime mental disorder is associated with four times the risk of having another drug abuse disorder[7]

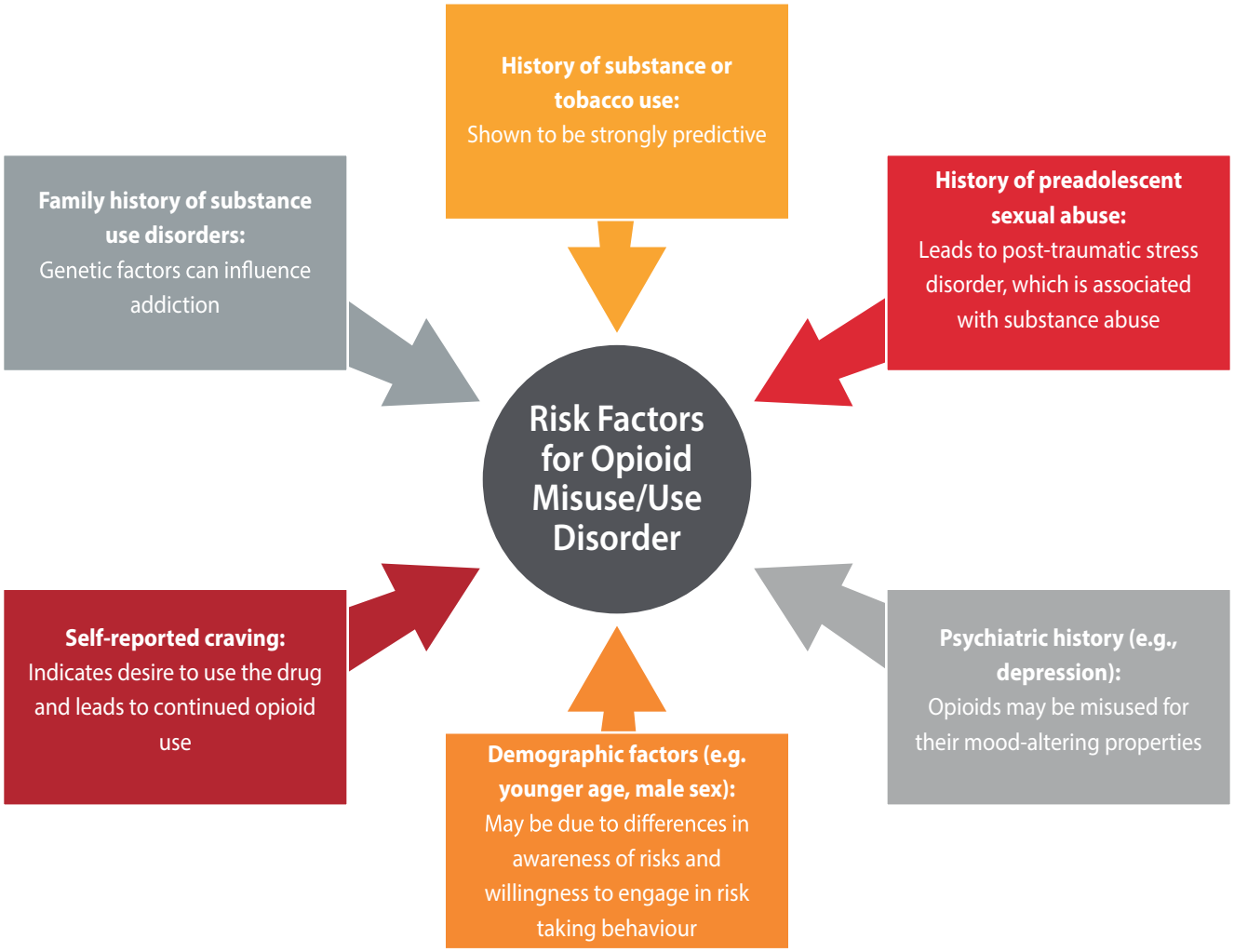
- Certain **opioid prescription** characteristics:
  - New prescription for any opioid with duration greater than 30 days[3]
  - A daily dose of greater than 120 morphine milligram equivalents[3] (see below for details)
  - Concurrent prescription of psychiatric medication, such as atypical antipsychotics (associated with highest risk) or anxiolytics[3]

Other risk factors in the literature that may indicate someone is at increased risk for opioid misuse/opioid use disorder:

- Demographic factors
  - **Younger age**[6]
    - ORT assigns age range between 16-45 years as a risk factor[8]
    - Results from an American National Drug Survey showed that drug dependence or abuse rates rise with age and peak in the twenties and subsequently decline at middle age[9]
  - **Male sex**
    - May be related to maturity, differences in awareness of risks and willingness to take risks[6]

- **Family history of substance use disorders**
  - History of alcohol abuse in the family with higher relative risk of abuse among males[10]
  - Prescription drugs may be weighed more heavily than other substances (endorsed by ORT) as there is evidence from one study that most of the genetic influence on heroin/opioid abuse is specific to heroin/opioids[11]

- **History of preadolescent sexual abuse among females**[8]
  - Leads to PTSD which is associated with substance abuse[6]



Reprinted with permission from Argoff et al. (2018).

Remember that this list is for opioid use disorder, but there are other potential harms of opioids including diversion and accidental overdose.

To elaborate further on the effect of higher doses, a study by Kaplovitch et al. found that patients escalated to high dose opioid therapy (defined as doses > 200mg of morphine or equivalent) were nearly 24 times as likely to die versus those patients who did not have escalated doses[12]. Risk of fatal opioid overdose has been shown with lower doses as well, with Canadian guidelines reporting risk as 0.1% for <20mg MED/day; 0.14% for 20-49mg MED/day; 0.18% for 50-99mg MED/day; and 0.23% for ≥ 100mg MED/day[4]. Not surprisingly, the risk of fatal overdose in patients with prior substance use disorder is even higher, with a 0.4% risk of fatal overdose at very low doses (<20 MED/day).[4] This risk increases at higher doses.[4]

Although patients on higher doses of opioids are at higher risk of adverse effects, such as increased mortality, consensus is lacking on whether high dose cutoffs should contribute to risk stratification.[12] Expert opinion considered using a high dose cutoff such as 120-mg morphine equivalent dose per day inadequate to identify high-risk patients alone as high doses may be a result of accommodating tolerance in some patients.[6,13] Further, patients predisposed to opioid misuse could be at risk of misuse with even low to moderate doses.[6]

The HARMS Program leaves it open to individual preference whether to include the opioid daily dose in risk stratification. It was also felt that calculation of morphine milligram equivalents per day would be onerous for some clinicians and so this is not a requirement of the program. However, your clinic could choose to include this, especially if your clinic had a non-medical staff member perform the calculations. Previous recommendation thresholds for "watchful" doses have included 50/90/200 morphine equivalents per day.[4]

To calculate morphine equivalents, see opioid conversion tables in Appendix B-8 of the Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain[4]: *http://nationalpaincentre.mcmaster.ca/opioid/cgop_b_app_b08.html*.

There are several additional considerations, beyond the medical history described above, that may contribute to making more accurate estimates of risk at initial assessment.

Baseline UDT:
Baseline UDT is recommended by several guidelines as it can indicate higher risk (it may indicate concern about a substance use disorder which, as described previously, puts someone at higher risk)

- Argoff et al. expert panel recommends definitive UDT (ie. LC-MS, GC-MS) at baseline for almost all patients with chronic pain being considered for an opioid trial as well as for ongoing monitoring of patients on opioids.[6] For those continuing opioid therapy from another provider, UDT should be completed within three months of the first office visit[6].
- *The Canadian Guideline for Safe and Effective use of Opioids for Chronic Non-Cancer Pain (2017)* states that clinicians may use baseline urine drug testing when considering patients for an opioid trial or for those who are currently on opioids. UDT can be repeated on an annual basis or more frequently for those at higher risk including those displaying aberrant behaviours.[4] However an abstract report, which is listed in the guideline as the formal study of urine drug screening for risk mitigation, reported no difference in rates of opioid overdose for those who did or did not receive baseline urine drug testing.[4] For those patients with chronic pain and a history of substance abuse, the Canadian guidelines recommend screening with a validated questionnaire (ie. CAGE for alcohol use, Current Opioid Misuse Measure (COMM) for opioid misuse) and suggest baseline UDT and periodically after.[4]
- *The CDC Guideline for Prescribing Opioids for Chronic Pain (2016)* found that there was limited evidence evaluating effectiveness of UDT for risk mitigation during opioid prescribing. Expert opinion does recommend that clinicians use UDT prior to initiating opioid therapy for chronic pain and periodically throughout therapy.[14] There is a lack of consensus on whether this should apply to all patients and the frequency of monitoring thereafter. Most experts agreed annual testing at a minimum for all patients. Previous guidelines suggested more frequent testing for patients at higher risk for substance use disorder, however experts thought it was difficult to reliably identify patients at low risk with currently available tools.[13,14]

Now that we've covered some of the factors that might raise someone's risk, let's look at some of the validated tools that have attempted to put this together in estimating someone's risk.

Risk Assessment Tools (Patient Questionnaires):
Some guidelines suggest utilizing risk assessment tools to assist the clinician in risk stratification and identifying risk of aberrant medication-taking behaviours.[13,14] However, there is limited evidence supporting the use of currently available risk-stratification tools and when Klimas et al. tested performance by calculating likelihood ratios, most screening tools demonstrated poor diagnostic performance.[3] The systematic review by Klimas et al. also found that commonly utilized risk assessment tools (Opioid Risk Tool, Brief Risk Questionnaire, Brief Risk Interview, and Screener and Opioid Assessment for Patients with Pain) were ineffective at discerning high from low risk patients.[3] There is a need for further clinical validation of existing tools and for the development of more accurate tools that include additional risk factors.[6]

As a result, expert opinion emphasizes the importance of understanding why specific risk factors predict risk of aberrant drug use, and that risk stratification with a tool is only one component of a comprehensive assessment. Thus, clinicians are encouraged to choose a tool that matches their preference and work flow[6]. Some commonly used tools to assess risks with opioid use include: the Opioid Risk Tool (ORT), Screener and Opioid Assessment for Patients with Pain- Revised (SOAPP-R) tool, Current Opioid Misuse Measure (COMM) and the Diagnosis, Intractability, Risk, Efficacy (DIRE) tool. A summary of a few commonly used tools with diagnostic accuracies (e.g. sensitivity and specificity) can be seen below with a more comprehensive table found in Argoff et al. (DOI:10.1093/pm/pnx285)[6]. Again it should be emphasized that risk stratification is not static as personal circumstances can change and thus should be reassessed regularly[6].

Opioid Risk Tool (ORT)	Description	Time to complete	Diagnostic Accuracy	Validated	Additional Notes)
Opioid Risk Tool (ORT)	Self-reported 10 item tool[15] that assesses risk of aberrant drug-related behaviours[16]	1 minute[13]	Sensitivity 20-99% and specificity 16-88% reported for detecting risk of opioid overdose, addiction, abuse or misuse using a cutoff score of > 4 or unspecified (5 studies)[14]	Yes[13]	
Screener and Opioid Assessment for Patients with Pain - Revised (SOAPP-R)	Self-reported 24 item tool[13] that assesses risk of drug-related behaviours[16]	< 10 minutes[13]	With a cutoff of >3 or unspecified - sensitivity 25-53% and specificity 62-73% for detecting risk of opioid overdose, addiction, abuse or misuse for likelihood ratios close to 1 (2 studies)[14]	Yes[13]	Designed to prevent patient deception[15] Requires licensing agreement but no fee for individual clinical use[13]
Screener and Opioid Assessment for Patients with Pain- 8 (SOAPP-8)	Self-reported 8 question tool that assesses risk for aberrant opioid-related behaviour[17]	< SOAPP-R (< 10mins)	Sensitivity of 74% and a specificity of 66%	Yes[17]	Adapted from the SOAPP-R to yield a shorter version while maximizing predictive accuracy[17]
Current Opioid Misuse Measure (COMM)	Self-reported 17 item tool to identify patients receiving long-term opioid therapy who are exhibiting aberrant behaviours[16]	< 10 minutes[13]	With a cutoff score of ≥ 10: Sensitivity 74% and specificity 73%, and with a cutoff score of ≥ 9, sensitivity 77% and specificity 66% for the detection of aberrant drug-related behavior (1 study)[15]	Yes[13]	Requires licensing agreement but no fee for individual clinical use[13]
Diagnosis, Intractability, Risk, Efficacy (DIRE)	Clinician interview 7 item tool to identify patients receiving long-term opioid therapy who are exhibiting aberrant behaviours[18]	< 2 minutes[13]	Sensitivity 94% and specificity 87% for poor vs good/fair adherence with a cutoff point of 13 (1 study)[18]	Yes[13]	

Table adapted from Argoff et al. (2018)

The HARMS Experience

There are a few practical elements that we have learned through experience when assigning someone's risk. Physician time is crucial, and most of us don't have time to manually apply validated risk stratification tools. At our clinic we tend to use clinical Gestalt (concerns about previous behaviour, medical history we are aware of with a focus on mental health and a history of addictions). Remember that this is an estimate! That estimate will be refined, so even if the estimate is off-the-mark, it can be refined over time as the patient declares himself/herself.

In a future version of the START-IT tool (see Chapter 7), we will be building optional, validated risk stratification tools into the program so that the information from these tools can be used without extra effort from the physician. Currently, the time to administer, compile and interpret the results from validated risk tools is too onerous for many physicians so this should overcome those obstacles.

In terms of how the risk estimates will be applied to real-life patients, the HARMS Program created various risk categories for patients prescribed opioids for CNCP (see Figure 2- HARMS Risk Ladder): low, medium, high and structured (very high). The general theme is that the higher the risk, the more frequent the UDT and the shorter the medication dispensing interval (i.e. high risk means tighter control). Structured resembles a hybrid between a high-risk pain patient, and a patient being treated for opioid addiction. For an explanation of how a given risk level guides UDT frequency, and why these numbers were chosen, see Chapter 4.

Once patients are risk-stratified, the physician notifies the clinical administrator of the risk levels for each patient. When first starting the program, we simply took the list from the EMR query, and wrote "high", "low" etc. beside any patient that would be part of the HARMS Program. As new patients are started on opioids or otherwise join the medical practice, we send a message to the clinical administrator for each patient saying "Please add to HARMS, [low/medium/high/structured] risk". Alternatively, you may prefer to label them by their levels as demonstrated in the Risk Ladder and Chapter 4.

Cases

Case 1

55 year old male was found through the EMR query and you know that the patient has CNCP, has been on a stable daily dose of morphine (40mg/day) for a long time, has an "appropriate" diagnosis, is employed, and as far as you know his history is negative for red flags. How do you approach risk stratification?

This patient, by clinical Gestalt, appears to be low risk. In the interests of your own time, you do not apply risk stratification tools, or a baseline UDT prior to initial risk stratification. If you have the time or clinical capacity to do these extra steps then it is certainly reasonable, but in our program it is not necessary. You message the clinical administrator and ask to add to the HARMS Program as Low Risk (or level 1, from Risk Ladder).

Case 2

A 58 year old female has just moved to town. Her previous records indicate that she has been on oxycodone/acetaminophen 4 tabs/day for several years for chronic back pain. There is mention of alcohol use disorder but it seems to be in long-term remission. Would you consider any additional steps when assigning an initial risk category for this patient?

This patient presents a greater challenge because you don't know her, and as a result your clinical Gestalt is "hazier". This is someone who may warrant a more objective marker of risk (in addition to the usual history and physical). We would consider doing a baseline UDT on this patient as a relatively simple objective test. In fact, we would strongly consider performing a baseline UDT in all patients prescribed opioids for CNCP who are new to your practice, as this can help guide initial risk stratification. Once UDT results come back, if expected benefits outweigh risks then you can assign a formal risk category as she enters the HARMS Program.

Case 3

A 43 year old male is new to town and you are to be his family physician. You have his old records which indicate that he is on 10 tabs of oxycodone/acetaminophen per day with numerous early refill requests as well as dose escalations. He lacks a good diagnosis (he has no-showed to numerous appointments with pain specialists and for imaging). He has a history of alcohol use disorder, child abuse, and he was previously on a methadone program. How do you approach this patient?

This patient is particularly challenging as risks appear to outweigh benefits and you are likely not going to offer this patient long-term opioid treatment for pain. Ordering a baseline UDT may therefore not be helpful (See Chapter 9) if in your clinical judgement his risks outweigh benefits already and the UDT result would not change that. If you think that a UDT result may actually change your approach, then you may ask the patient to provide one. Consider that if UDT is unexpected this may make the ensuing conversation easier, however if UDT is expected then it may make the ensuing conversation more difficult if you are uncomfortable prescribing long-term anyway and will not offer patient this treatment option. The challenge in this scenario is not in deciding exactly what to do with his opioids, but instead how you do this. Critically important at this visit is compassion and open communication with the patient. The goal is to build/maintain a therapeutic relationship, as you adapt your treatment strategies to his suffering. See Appendix VI-VIII. If you establish that he is indeed addicted to opioids and he acknowledges this, then offering him in a non-judgemental way help for this (with OAT) so that he doesn't have to go through withdrawal may be enough to establish an initial therapeutic alliance.

Chapter Pearls

- Risk stratification is critical in guiding how systematic UDT (the HARMS program) is applied for a given patient. We want to prioritize safety while also acknowledging patient convenience. This means more frequent UDT for higher risk patients, and less frequent UDT for lower risk patients.
- Remember that our observations of behaviour are not sufficient to exclude people at risk, and patients can withhold information about illicit drug use.
- The initial risk stratification is an estimate based on information at one point in time. It will be refined over time in response to UDT results and other clinical observations.
- HARMS is meant to be practical - when it comes to risk stratification, use what you have time for. We don't routinely use validated risk stratification tools in our practice. However this may change with the automated application of these tools coming in a future version of START-IT.

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Now that HARMS Program patients have been identified and risk stratified, we need a system to keep this organized and make sure that UDT is actually happening at a frequency corresponding to risk...

Patient Master Lists - Creation and Maintenance

Now that patients have been selected for the program and risk stratified, creation and maintenance of a master list is critical to ensure that UDT is happening at a rate corresponding to that risk...

Creation and maintenance of a master list for patients in the HARMS Program is important because it will dictate who is getting selected for UDT and how frequently. The master list keeps track of all the patients in the program, including each patient's assigned risk category. The list will be used to randomly select patients for UDT. At our clinic, we keep track of patients in an Excel spreadsheet on a password-protected computer. This spreadsheet is also able to randomly select patients at the appropriate frequency and organize names into a user-friendly manner for the booking staff to book UDT appointments.

The master list is a living document with patient names being added and removed as they enter and exit the program, and risk categories being updated. Patients that have failed to provide UDT despite being selected are kept on a "recall" list in this document to ensure they don't fall through the cracks. Keeping this one document updated ensures that appropriate patients are getting booked for UDT, and inappropriate patients (like those who have left the program and are no longer on opioids) are not.

By the time of master list creation, the patient lists initially generated by the EMR query have been evaluated and trimmed by the physicians, with risk estimates assigned to each patient. Initial master list creation is most easily done by taking these completed lists of names and risk categories from each physician and simply entering them into a common spreadsheet such as this one. The risk category can be selected from the drop-down menu. Note that Level 1 and 2 are both considered low risk and for the purposes of randomization make no difference (the only difference is in the opioid dispensing interval). The Recall List is organized on its own tab at the bottom. The Recall List keeps track of patients that despite being randomized are not providing a UDT for whatever reason (see Chapter 5). For details on how to use the spreadsheet to randomize patients for UDT, see Chapter 4. When first opening the Excel spreadsheet, you may get a "SECURITY WARNING: Macros have been disabled" message. Simply click "Enable Content" which allows the formulae we have designed into it to be functional.

Once the initial list is created, several situations will arise:

Adding a patient: for new patients, add the patient name at the bottom of the list and select the appropriate risk category from the drop-down menu.

Removing a patient: when a patient is removed from the program simply delete his/her row. The message to remove the patient from HARMS should only be conveyed to you by the prescribing physician. If a patient claims they are no longer on opioids when being phoned for a UDT, verify with the prescriber before removing the name. In our experience, it is not uncommon that patients come off of opioids and the physician is either unaware, or forgets to notify the administrator to remove.

General maintenance: once per year, consider routing a list of patients in the program to their MRP. This gives physicians a chance to remove names that shouldn't be there. You also may consider using an EMR query on a yearly basis to detect patients that should be in the program who are not (similar to the strategy used in Chapter 1). At our clinic, we felt this yearly EMR query was low-yield since it has been engrained in all of the physicians to reflexively add any new patients on opioids to the program.

Depending on the clinic preference, you may consider having an agreed-upon place in the chart where a patient's enrollment status and risk level can be found. This makes it easy for anyone looking at the chart, to know if the patient is already enrolled in HARMS, and to refill an opioid prescription. In our OSCAR EMR, we write a single line under the "Reminders" section that says HARMS Program and a risk level. To make this process as streamlined as possible, the physician messages the administrator a risk level "HARMS, Level 3" when adding a new patient to the p

program and the administrator then adds the patient to the master list, *and* writes the line under the Reminders section. Likewise, when removing a patient, the physician messages the administrator who then takes the patient off the master list and removes the note in the Reminders section. We have heard of other clinics adopting HARMS and creating their own toolbars to organize all of this information (and more) automatically. You may contact Joyce Stansell, Quality Improvement Decision Support Specialist for numerous Northern Ontario Family Health Teams, at jstansell@ndfht.ca. Joyce would be happy to share the HARMS Program tools they have created in Nipigon for PS Suite. For a handout on the tools they have developed to simplify the HARMS Program for Telus PSS, see www.harmsprogram.ca/TelusPSS.

Chapter Pearls

- The master list is where all of the HARMS Program patient information is organized that will dictate who is randomized for UDT and how often. It can also be seen as the interface between clinicians and administration, so it's important that clinicians update administrators when changes need to be made, and administrators notify clinicians when concerns arise (ie. patient says they are no longer on opioids, or not providing UDT - see Appendix II).
- Consider using our spreadsheet to keep track of patients and to randomize them in a user-friendly manner at a rate concordant with their risk category.
- If using TelusPSS EMR, then consider utilizing the HARMS Program toolbars developed by our colleagues in Nipigon.

Now that we have a patient master list, the next step will be selecting patients for UDT. . .

UDT Selection

Now that we have all of our HARMS Program patients risk-stratified and on a master list, the next step is actual selection for UDT...

While HARMS was designed to apply UDT in a randomized, risk-concordant fashion, there are times when it is appropriate to do "non-randomized" UDT. Namely, if a physician has clinical concerns for whatever reason (early refills, deteriorating social function, etc.) then he/she may request a UDT. Therefore, two types of UDT can be ordered - randomized (through HARMS) and non-randomized (typically clinician concern or baseline UDT for a new patient).

Randomized: this is the core of the HARMS Program UDT system. We use computer randomization to select a patient for a certain number of months per year to provide a UDT. The number of UDT is based on risk category, with low risk patients getting selected for one month per year, medium risk patients two months, and high-risk patients six months. This is based partly on the following expert recommendations.[1]

- At least annually for low risk patients
- ≥ 2 times per year for moderate risk patients
- ≥ 3 per year for high-risk patients
- Additional monitoring at any level per clinical judgment[1]

Given the significant gap between the recommendation for medium risk (2 times/year), and our "structured" stream (2-4 times/month), we felt as though the high-risk patients should be subjected to 6 times/year so we chose this instead of "≥3".

We also wanted the capacity for additional randomization so that, in theory, anyone in the program could be selected any month. This would mean that anyone could be selected at any time, whereas if we didn't do this then a low-risk patient selected in the first month of the year would know that there are no more UDTs for the next 11 months. We therefore added an option to randomly select a small number of patients (5%) each month, in addition to the 1/2/6 months per year already randomized based on risk category. This is also built into the randomization spreadsheet and is found on the UDT Selection List tab.

Non-randomized: these UDT are typically fairly straight-forward. If a physician requests a UDT (due to an observational concern, baseline UDT for a new patient, etc.) then a UDT may be requested independent of the above randomization algorithm. At our clinic, we do this by sending a message to administration to book a patient for UDT. The patient can then be manually added on to the list for the coming month. The other time where a patient may provide a non-randomized UDT would be if he/she is in either the structured risk category (Level 5) or opioid addiction (Level 6), in which case he may be providing UDT on a scheduled basis (i.e. every 1-2 weeks, monthly, etc. depending on individual physician preferences). With these structured UDT, we have found it helpful to put the onus on the patient with clear instructions that he/she is responsible for booking UDT and attending them at regular intervals.

In terms of actually generating the randomization list, we would strongly recommend using the spreadsheet tool that we created and currently use in our clinic. That document has explanations about how to generate patient lists for booking staff each month that ensure randomization frequency is concordant with risk category, and to simplify the whole process as much as possible.

Note that there is significant variability in how you may go about informing/consenting patients to be a part of your HARMS Program. At our clinic, we rolled the program out slowly and had a discussion with each patient as part of a routine medical visit. As part of that discussion, we completed a treatment agreement that included consents around UDT and the HARMS Program. See Appendix A and I for more information.

Chapter Pearls

- While HARMS was built to support randomized selection for UDT, if a concern exists then the physician can (and should) still message clinical administration to book a "non-random" UDT.
- Consider using the spreadsheet that we created - and use currently in our clinic - to both maintain a master list and generate patient lists to provide random UDT.

REFERENCES:

1. Argoff CE, Alford DP, Fudin J, et al. Rational Urine Drug Monitoring in Patients Receiving Opioids for Chronic Pain: Consensus Recommendations. *Pain Med Malden Mass*. 2018;19(1):97-117. doi:10.1093/pm/pnx285

Now that names have been selected for UDT, we will go over how the booking staff notifies patients of the UDT appointment and what to do in the various situations that may arise . . .

Contacting the Patient and Booking UDT

Now that a list of patients has been generated to provide a UDT, let's go over the booking procedures...

Your clinic will have to decide on whether it would like to do point-of-care testing (IA), and/or confirmatory testing (LC-MS), as well as how appointments will be structured at the clinic. See Appendix i for considerations when making these decisions. At our clinic we use both methods of UDT, and hold two UDT clinics per week (½ day each).

The following assumes your clinic has the capacity and desire to do IA urine drug testing. If it does not, the same protocols can apply except instead of providing a UDT at the clinic, the patient can either provide one for LC-MS directly at the lab, or at the clinic which in-turn sends the sample to the lab for LC-MS analysis.

At this point, the UDT selection process (Chapter 3) has generated a booking list for the month, and these patients will be booked at some point in the coming month. There will also likely be a list of patients on the "Recall list" from previous months that have not provided UDT despite being selected. If your clinic holds 8 UDT clinics per month, then patients on these lists could be divided roughly equally between the clinics. The patient is phoned the morning before the planned appointment. Ideally, UDT will be provided within 36 hours (i.e. same day or next).

For suggestions on how to handle the various situations that may arise when phoning patients see the schematic on the next page.

While not depicted explicitly here, if you are unable to even reach the patient after numerous attempts (answering machine, no phone, etc) then you will place the patient on the recall list so that he/she will not "fall through the cracks". You will also message the physician for further instructions. While we don't provide a "hard and fast" number, if you have tried at least 3 times over 2 weeks and been unsuccessful at reaching the patient or hearing back from them, then consider adding them to the recall list and messaging the physician.

Cases

Case 1

You are the administrator for the HARMS Program at your clinic and Mr. Smith is randomized to be selected for this month. You call the number on file and the patient answers. You tell him you have an appointment for him tomorrow to provide a UDT. He says he doesn't have to do UDT, and that his physician never spoke to him about it. How do you respond? *This scenario was rare at our clinic, as all patients in the program had already had a discussion and signed a treatment agreement and consent. If your clinic was unable to do this however, then it is still worthwhile to follow the schematic, which in this case will likely lead to messaging the physician for further instructions. Physician may then discuss the program with the patient to initiate the process for consenting +/- completion of treatment agreement.*

Case 2

You are the administrator for the HARMS Program at your clinic and Mr. Johnston is randomized to be selected for this month. You leave a message on the voicemail to call the clinic back. He doesn't call back, so you call him again the following week and leave another message. He still doesn't call back. What do you do at this point? *Consider trying one more time, or trying an alternate phone number, and if still no response then add him to the recall list (will try again next month) and consider notifying the physician.*

Tips and Suggestions

Start of conversation: "You've been randomly selected through our opioid safety program to provide a urine drug test. This program applies to all patients at our clinic prescribed opioids for chronic pain. We will try and book you within the next 1-2 days, are you able to attend an appointment tomorrow?"

Patient asks why he/she has to do UDT, say: "Our clinic is using urine drug testing for everyone at the clinic prescribed opioids for chronic pain. It is a safety measure given the potential harms of these medications. Testing selection is random, and typically infrequent. "

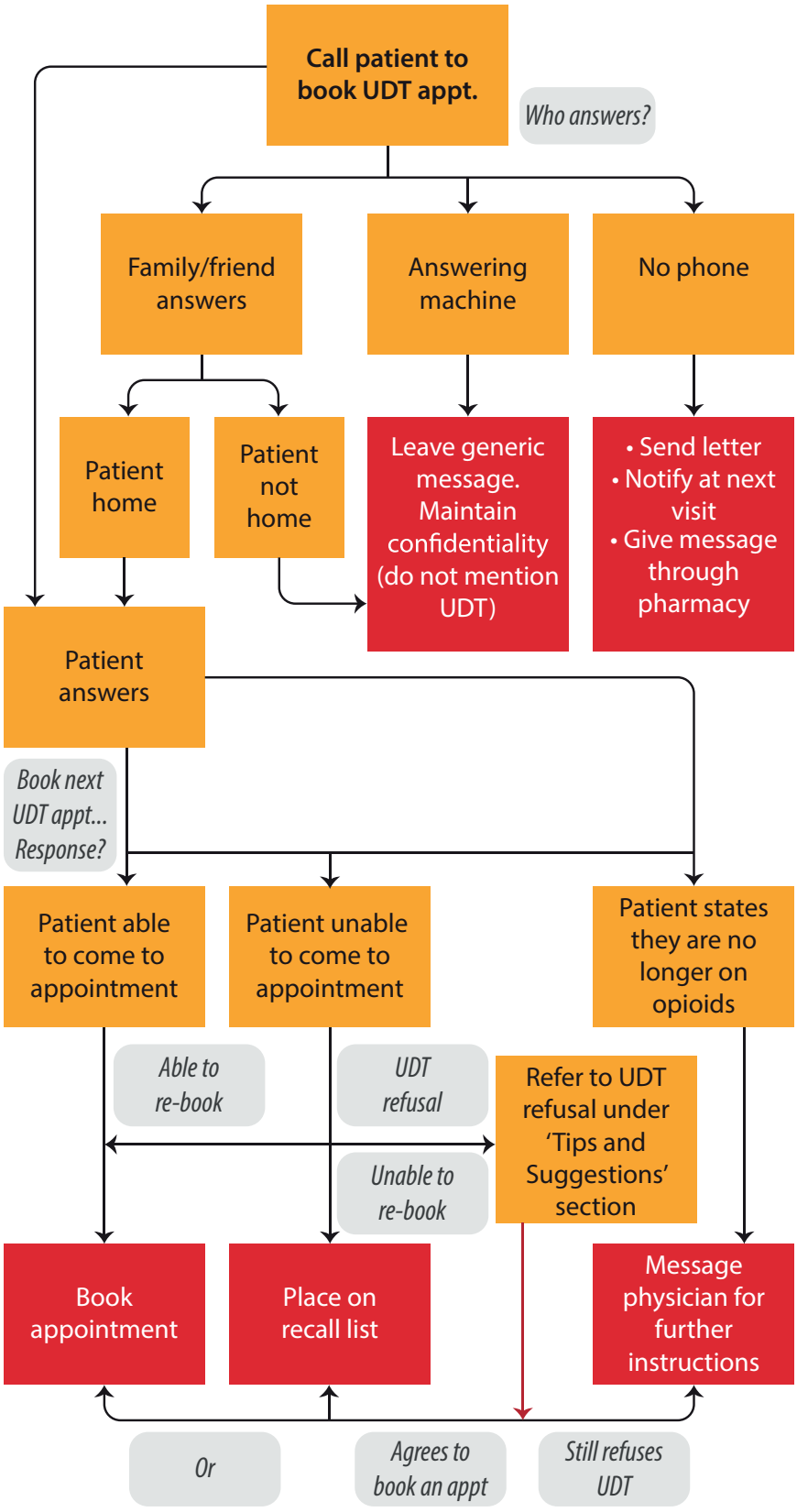
Patient refuses UDT: "You're aware that this is an expectation of patients at our clinic prescribed opioids for chronic pain? I will notify your physician - is there a particular reason you would like me to tell him/her about why you are declining to provide a UDT?"

Other Reminders

Patient does not book an appointment (for whatever reason) - make sure to add to recall list of Randomization spreadsheet.

Updating the master list: once patient is booked for an appointment, consider marking this by bolding the name on the UDT Selection tab for that month. That way you will know who still has to be booked. If patient ends up cancelling that appointment (or no-showing) and not re-booking right away, add the patient to the "Recall list" (See Ch. 3).

A note about notification time: while ideally the patient is booked in <36h from the time of notification, this is of course not always possible (work commitments, etc). If patient is unable to make this, then book for next time when patient is available. If not available to come to clinic within the next several weeks, at the discretion of your own clinic HARMS policy (See Appendix i: Choosing a method for UDT), you may offer to the patient to provide a UDT at the lab (they tend to be open more hours than UDT clinics). Patient can either pick up requisition at the clinic, or as applicable have req sent directly to their lab.



Chapter Pearls

- UDT has the potential for significant inconvenience for patients (hence why for low risk patients where safety is less of a concern, it is conducted infrequently). The 36 hour from notification to provision of a sample is a goal, but is not possible in everyone. In these cases, book when it's convenient for the patient.
- The Recall list is an important way to keep track of people that are randomized but not providing UDT. In our original experience, patients like this would often fall through the cracks. Perhaps ironically, but not surprisingly, the patients that are consistently busy, cancelling and no-showing are the ones who are often eventually identified as being "harmed".

Now that patient is booked for a UDT, let's cover how the UDT may be conducted at the clinic...

UDT Collection and IA Analysis

Now that patients are booked for UDT, we will cover considerations for conducting UDT in the office...

Most primary care clinics are not set up to collect UDT (protocols for providing the sample, anti-tampering measures, testing kits, storage of samples, sending to the lab for confirmatory testing, etc.). This section assumes that the UDT is being conducted, and analyzed with IA, on the clinic premises. Note that depending on clinic preferences and patient circumstances, you may consider allowing patients to provide the sample directly at the lab.

Clinic Setup

As discussed further in Appendix I, consider holding "UDT Clinics" a few half-days per week, in which patients are booked sequentially in blocks. This will minimize the effort of setting up the washroom repeatedly as would be required if UDT appointments were booked sporadically throughout the week. We book patients every 20 minutes but in our experience the appointment typically takes less than 10 minutes. Ideally there is a washroom within the clinic that can be used solely for UDT for the duration of the UDT Clinic; this washroom should be close to an exam room. To prepare the facilities for a UDT clinic, we place an "out of order" sign on the door so that its use is reserved during that time for the UDT appointments. Your clinic may also consider anti-tampering strategies which are discussed in Appendix III (blue water, taping faucets, etc.).

START-IT Tool for Simplified UDT

We would strongly encourage you to consider using START-IT to facilitate UDT in your office. We developed this tool, have used it in our own clinic for years, refined it, and share it freely with others. Described further in Chapter 7, START-IT is a program on a tablet PC that simplifies nearly every aspect of UDT in the primary care clinic. Among others, START-IT collects information important for the interpretation of the UDT including prescribed opioid and last dose, non-prescribed drugs/medications, and results of the IA UDT. Prior to this, we collected patient self-reports on paper which created numerous extra steps for physicians and administrative staff alike. A future version of START-IT is also planned to have the capability to automate numerous other components of UDT and Chronic Pain management such as risk stratification, UDT consent, Brief Pain Inventory, and more.

Patient Arrival

For discreteness, appointments are conducted very similar to any other appointment. When patients arrive, they first register for the appointment and wait until they are called into an exam room. We welcome the patient and explain the nature of the appointment if it's the patient's first time, and then start using the START-IT tool. If consent is going to be collected with every UDT visit, then the future START-IT tool will be able to facilitate this. Historically we have not been collecting consent at each visit as we obtain a single consent when starting the program, however we would recommend considering it in the future (Appendix ix).

We start by completing the initial parts of START-IT on the tablet PC – prescribed medication and self-reported drugs/medications not prescribed. When applying START-IT, it is important for the clinic employee to verify the prescribed medication (either by entering it personally or double-checking in the EMR what the patients enters). This is a necessity as the START-IT interpretation will assume this information is accurate. For example, if a patient that is not prescribed oxycodone claims on START-IT that he/she is, then when oxycodone shows up in his/her urine it will appear to be expected.

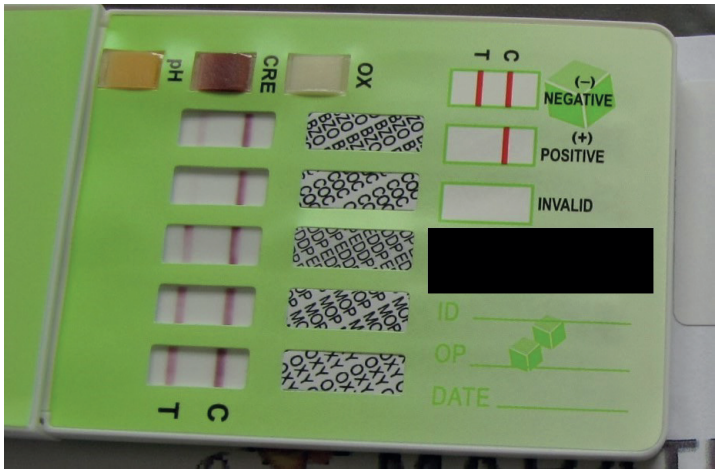
The patient will then be asked to provide a urine sample.

Provision of UDT

The patient is given a urine-specific container and escorted to the washroom. We use the same containers that are used for urine C&S samples. He/she is asked to provide enough fluid to fi ll the specimen co ntainer to the black line, which is 30mL. In our experience however the lab has been able to process less than 30mL. The patient then brings the sample back to the exam room where it will be analyzed.

Analysis of UDT

The sample is analyzed with the IA panel(s). Insert the panels into the specimen container (we have to squeeze the container to bend it so that the whole UDT panel kit will fit inside). Leave the panels in for 10-15 seconds. Most panels will have "positive" (a single line), "negative" (a double line) or "invalid" (no lines). Note that even if the 2nd line is very faint, this is still a 2nd line and is considered negative.



If using anti-tampering measures, the temperature should be checked within the first 4-5 minutes of provision and should be 32.2-37.7C. Also urine can be dipped for Creatinine/Specific Gravity/pH.

In the rare case where there is an invalid UDT (as indicated by the "invalid" bar on the IA), repeat the test immediately (on the same sample first in case it was simply a defective IA dip). Similarly, if one of the tampering indicators was abnormal, ask the patient to urinate again if possible and repeat the test.

Patient Debrief

Show the patient the IA results, and enter them into START-IT along with the indicators for tampering as applicable. With the click of a button the report is deposited into the patient's chart in the EMR (assuming OCEAN platform is being used, and you have one of the compatible EMRs). If there is an unexpected result, the patient may have an explanation which you can pass along to the physician. For other aspects of handling "unexpected" results, see Appendix II.

Patient Fails to Attend

Also of note, if a patient is booked for a UDT but does not attend the appointment (no-show, cancellation), then the patient should be added to the recall list in the Randomization Spreadsheet (your masterlist document - Chapters 2-4). Similarly, if the patient says that he/she is unable to urinate, you can either add them to the recall list, or if the schedule permits, keep the patient in the clinic drinking water and simply obtain the sample later in the clinic. For how to respond to repeated failures to attend, see Appendix ii.

Cases

Case 1

You wonder about whether you should do LC-MS and/or IA, at the office or at the lab? *There are several considerations here including human resources, patient distance from the clinic/lab, and pros and cons of both tests. Clinical policy decisions such as this are discussed further in Appendix I.*

Case 2

The patient has provided a urine sample and you are analyzing it. BZD has a very faint 2nd line. Is this positive or negative? *This scenario comes up repeatedly - as long as you can see that 2nd line, the result for that panel is negative (even if very faint).*

Case 3

Are taping and temperature taking really necessary? *We have been doing this for greater than 5 years now and have only had one temperature that was too cold, and no abnormal results for creatinine, specific gravity or pH. You may consider not using these given their apparently low-yield. See Appendix III - Anti-tampering Techniques.*

Case 4

Our clinic is unable to use START-IT - how should we collect and conduct IA in the clinic?
This is challenging but possible. Prior to creating START-IT, we used paper self-reports which also had a section where the staff conducting the test could write IA results. We then had this paper scanned to the chart and interpreted by the physician. We have START-IT available online (www.harmsprogram.ca/START-IT-Tool) that does not require the OCEAN platform, in which case you can do START-IT in a web browser and then copy and paste the interpretation into any EMR chart.

Chapter Pearls

- Organized collection of not just the UDT itself, but prescribed and non-prescribed medications, are important to ensuring an accurate interpretation.
- UDT can be conducted in a discreet and humane manner.
- Be careful if the patient asks what a result means - if you are not trained in UDT interpretation then it may be worth leaving to the physician. There are false positives (ex. morphine panel is positive even when he/she didn't actually take morphine), and false negatives (ex. oxycodone panel is negative even when he/she took oxycodone recently).
- A urine sample must be labelled correctly. In the case of LC-MS, as accurate as it is, if the label is for the wrong patient then you will have erroneous interpretations and potentially disastrous management changes. Preventing results from going under the wrong patient is one reason it is helpful to both input the initials into START-IT (to prevent human error of uploading to the wrong patient chart), and to show the result to the patient so that there are no surprises and he/she can accept or deny the result implication on-the-spot.
- If technical questions arise, feel free to contact our Addictions and Pain Care Coordinator at apcc@mfht.org. This staff member has a wealth of knowledge about the technical process of conducting UDT in the office and has been doing it at our clinic for years.

Now that UDT has been collected and analyzed, let's look more closely at the START-IT tool for automated IA interpretation...

START-IT Tool for Automated UDT Interpretation

Let's take a closer look at how your clinic might be able to use the START-IT Tool to simplify urine drug testing (UDT) in your clinical setting...

In clinical use since early 2018, START-IT is applied at the bedside on a tablet PC by a non-medical clinical employee (i.e. no special medical designation is required). The START-IT Tool was designed to simplify UDT, including automating as much of the process as possible.

Since START-IT was initially created, it has evolved quickly to suit the needs of frontline clinicians and will soon simplify nearly every aspect of UDT in the office. START-IT collects all of the required information to interpret a UDT immunoassay (IA) test, including but not limited to: prescribed opioid and last dose, self-reported non-prescribed medications/ drugs, and UDT IA testing results. START-IT then automatically interprets the test using best-evidence, and the report is uploaded into the EMR with the click of a button. START-IT gives explanations about limitations for that specific UDT result, including reasons for false positives and false negatives as applicable. START-IT also makes tailored recommendations about when to send the sample for further "confirmatory" testing (LC-MS), and facilitates tracking data digitally for quality improvement and research. Additional options in development also include having START-IT obtain patient consent, apply a validated risk stratification tool, and apply and calculate a Brief Pain Inventory. It is planned that it will also have the capacity to apply a one-time opioid treatment agreement (if desired). Reports will even be customized depending on whether the UDT was being conducted for chronic pain, opioid agonist treatment, or as an employee requirement. START-IT does all of this with no paper, no scanning, no delays, no errors in interpretation, and no time from the physician.

While START-IT has always been free (we have never charged a fee), a membership with OCEAN was previously required because its platform was needed. This however had recently changed and we are able to host START-IT on our website. We are grateful to the team at CognisantMD (makers of OCEAN) for their help in making it available for free from any internet browser, without an OCEAN subscription. Of course, the EMR integration is not available with the browser option, so in this case there will be a few extra steps (copying and pasting into the EMR), and automated data collection would not be possible.

As we delve more into how START-IT works and what it does, let's start with an example of a final report. This gives a "big picture" perspective on how the information in START-IT can be used clinically. We'll then cover the various steps of setting it up in your office and applying it in patient encounters.

Sample report for START-IT 2019: *This assumes that a patient is prescribed morphine, reports last dose <24h ago, does not report any other drug use, has IA tested with a standard 5-panel IA (in this case – morphine panel, oxycodone panel, EDDP (methadone) panel, cocaine panel and benzodiazepine panel), and all panels are negative.*

START-IT Automated IA Urine Drug Test Interpretation

OVERALL INTERPRETATION: UNEXPECTED. Morphine is prescribed and should be detected on today's test (last dose reported <24h ago), however it was not detected (unexpected result). Given that patient reports are inconsistent with the result obtained here, confirmatory testing (LC-MS) would be strongly recommended. For detailed IA interpretation see "Interpretation Details" below.

TESTING CAPABILITIES and LIMITATIONS: With the IA panels used today, the following drugs would typically be DETECTABLE: morphine/codeine/heroin, oxycodone, methadone, benzodiazepines (with the exception of clonazepam and lorazepam), cocaine. The following drugs are VARIABLY DETECTABLE: hydromorphone, hydrocodone, clonazepam and lorazepam. The following is a list of drugs that would be UNDETECTABLE: fentanyl, tramadol,

buprenorphine, barbiturates, amphetamines, methamphetamines, MDMA, cannabis, phencyclidine (PCP). Explanations for the more common examples of false positives and false negatives relevant to today's test are explained under "Interpretation Details" below.

PATIENT BACKGROUND: Patient initials: RM. Pain Diagnosis: Chronic Back pain. Risk Category: LOW. Initial Selection Method: Random. Notification period: <36h. From recall list? No.

PRESCRIBED MEDICATIONS: Morphine (last reported <24h ago).

SELF-REPORTED NON-PRESCRIBED MEDICATIONS: None.

UDT IA PANEL RESULTS: Morphine panel NEGATIVE; EDDP (methadone) panel NEGATIVE; Cocaine panel NEGATIVE; Oxycodone panel NEGATIVE; Benzodiazepine panel NEGATIVE

INTERPRETATION DETAILS:
MORPHINE (UNEXPECTED): Patient is prescribed morphine which should be detected with the IA panels used on this sample. The negative result is therefore unexpected, and is also inconsistent with patient's last self-reported dose (patient reports last taking <24h ago which would typically be detected on this test). This raises concern that patient has actually not been taking the prescribed morphine (detection window approximately 3-4d). Explanations for a true negative result include that patient is taking too much of the medication early in a refill and so hasn't taken it recently, or result may indicate that patient is diverting the medication. False negatives (negative results when the patient is actually taking the medication) are rare for morphine, however can be caused by: very dilute urine, dose being too low and/or medication being metabolized so rapidly that it is not detected (note that morphine IA tests have very low detectability thresholds so these reasons are unlikely).

ACTING ON UDT RESULT: Before acting on any UDT result, it is important to understand the limitations of the testing, and that they can inform – but are not a replacement for – the Clinical Gestalt. The intent of UDT is not to punish patients, but to inform the risk/benefit balance and facilitate open discussion. Discussion with the patient about today's results should be used to guide any changes that need to be made to the morphine prescription.

If you are still unsure of the significance of this UDT result - and/or if you plan on making significant changes to patient's management based on this result - then strongly consider incorporating LC-MS results and/or the input of a clinical biochemist prior to discussing with the patient.

DISCLAIMER: The authors of START-IT have done their best to incorporate best-evidence into this tool. Beta-testing has been done to ensure accuracy however errors can occur. If you do note an erroneous interpretation, please notify us at info@harmsprogram.ca and we will work to correct the problem. Furthermore, the authors take no responsibility for the actions you take based on START-IT reports– clinical judgement and your own verification of what results mean supersede any recommendations given here.

Explanations of each of these sections are as follows:

- **Overall interpretation**: The overall interpretation is expected, unexpected or equivocal with a brief explanation about each medication/drug relevant for this test. A recommendation is given on how important confirmatory testing is for this specific test, largely based on degree of discordance between patient's reports and test results, but also addressing general limitations of IA.
- **Testing Capabilities and Limitations**: Summary of what drugs/medications are detectable, undetectable, or variably detectable based on the specific combination of panels used on today's test. In general, we used a sensitivity of >= 75% for detectable, <10% for undetectable, and 10-74% for variably detectable.
- **Patient background**: relevant demographics, risk category, selection method, etc. This section is mostly relevant for research but also gives a very brief clinical summary of the patient. The initials are there for safety assurance to make sure that the report isn't accidentally uploaded into the wrong patient's file.
- **Prescribed medications**: relevant medications (opioids, other controlled substances) that patient is prescribed and last dose
- **Self-reported non-prescribed medications**: medications/drugs that a patient is not prescribed but wants to self-report.

• **UDT IA Panel results**: the actual results of IA testing. This is also a safety assurance in case there's a bug in START-IT with the interpretation, because you will be able to see the actual test result.

• **Interpretation details**: the details of why UDT was interpreted this way, with specific explanations, are provided here.

• **Acting on UDT Result**: reminders about the importance of applying this result to your patient, and that UDT informs your clinical picture but is not to be used in isolation. In general, if you're not sure, verify what results actually mean, and then discuss with your patient in a non-judgmental manner.

• **Disclaimer**: a reminder about the limitations of IA in general, and the START-IT tool

START-IT Initial Set-up

If planning on using START-IT with the OCEAN platform, then the process is really three parts: tablet set-up, OCEAN set-up and START-IT set-up.

• For set-up of hardware and software, if using with OCEAN platform we would recommend you check out https://support.cognisantmd.com/hc/en-us/sections/115000861952. Once you have OCEAN and the tablet, simply add the form "START-IT" (publicly available) within OCEAN.

• It is worth testing on a dummy patient in the EMR chart first to make sure that everything goes according to plan. Little glitches may come up in the beginning. If you are a subscriber to the OCEAN platform, feel free to contact them at: info@cognisantmd.com

Note that we are not affiliated in anyway with OCEAN/CognisantMD.

Using START-IT for patient encounters

Now that START-IT is set-up, you're ready to start applying it with real patients. Check out our website for screenshots that show the latest version and examples of how the tool is applied at the bedside.

Let's give a brief explanation of how the interpretation algorithm built into START-IT works. START-IT looks at a variety of factors to make a final interpretation of either "Expected", "Unexpected", or "Equivocal". The distinction is based on what medication(s) is prescribed and claims of the last dose, any self-reported non-prescribed medication(s) and claims of the last dose, the detectability of these drugs of interest for this particular IA (detectable, undetectable, variably detectable), the detection window (how long a drug is expected to be detected in the urine) and the actual IA result (positive or negative).

• An *expected* result means that the patient's UDT result is consistent with prescribed medication(s) and last dose, and there were no non-prescribed drugs of concern either self-reported or detected on IA. Note that START-IT *never* considers cannabis unexpected (even if it is not prescribed).

• An unexpected result means that either i) there was a drug(s) of concern that was self-reported and/or detected on the IA that is not prescribed, or ii) the prescribed medication that should have been detected based on detectability of the test and patient's self-report was not detected.

• An equivocal result describes that grey area where there is a soft concern but not enough to call it unexpected. An example of this would be someone who is prescribed a detectable medication, but claims not to have taken it recently, and not surprisingly it is not found in the urine. This result could be concerning (perhaps the person is diverting his medication), or alternatively perhaps the person has intermittent pain and has good reason to have not been taking it.

There are over 200 different "results" for the specific interpretations - four types of "expected", nine types of

"unexpected", and five types of "equivocal" based on prescribed vs non-prescribed, detectable vs non-detectable vs variably detectable, last dose reported, and actual IA result. The different types of results can be stored in the OCEAN database (if you subscribed for "studies") and then analyzed for QI and research.

Comments are customized based on reported sensitivities and specificities in the literature as much as possible. Note that there is significant variability in the literature with these numbers. There is also significant variability with detection windows for the various drugs, and causes of false positives for the various panels. Comments in the START-IT report are meant to acknowledge this ambiguity as much as possible and provide the information that a clinician would want to know when trying to ascertain what a result actually means.

Note that we do not attempt to evaluate urine quantitatively. While it seems logical to look at the strength of the dose and the specific time since that last dose, and evaluate what concentration is in the urine to determine if the person is taking more or less than prescribed/claimed - this approach is limited by significant variability between people and resultant room for error. There is so much variability between people in drug absorption, metabolism and excretion that the practice of quantitative evaluation, as we see it, is over-complicating the issue and potentially leading to drawing erroneous conclusions. That said, on a case-by-base basis, use common sense. If a patient is prescribed oxycodone at a low dose infrequently, and oxycodone panel on IA is negative, then there is a very good chance this is a false negative. As START-IT will tell you, the sensitivity of the oxycodone panel for oxycodone is on-the-whole only about 75% and the test would have lower sensitivities for lower, infrequent doses.

Information for the person administering START-IT:
What to do with the following results:

- When considering what to do with the result -"unexpected" - see Appendix B
- "Equivocal" - suggest messaging the physician as depending on the specific situation and physician, some may be alarmed and want to discuss with the patient while others may not
- "Expected" - typically no action needed unless your clinic has a system built-in to bill for these in which case physician typically has to acknowledge the interpretation (Appendix D).

Data Compilation
If using START-IT with the OCEAN platform, then it is possible to easily track the information in START-IT digitally for QI and research purposes. While we do not charge anything to use START-IT (if using on the OCEAN platform then the company that runs it - CognisantMD - does have a monthly fee), we ask that clinics using START-IT give us permission to use their de-identified data for evaluative purposes. Any research will of course be conducted with Research Ethics Board (REB) approval. There are a few simple steps to setting up data tracking.

Please contact us if you will be using START-IT at your clinic so that we can give you the password, and help you get set up with data tracking for your QI purposes (QI does not require REB approval). As mentioned, if we are going to have access to the numbers (for research purposes) then we would need REB approval beforehand and would obtain it as applicable.

Chapter Pearls

- START-IT can greatly simplify the entire UDT process.
- START-IT reduces consumption of human resources in numerous ways: no printing or scanning of consents, self-reports or results; no time on the part of the physician looking up specific results for sensitivities, specificities and false positives/ negatives; data on UDT is stored digitally so can be easily analyzed for QI and research purposes.
- By automating UDT interpretation, START-IT is expected to prevent errors in interpretation and subsequent errors in management.

While START-IT can do most of the work for you when it comes to IA interpretation, the next chapter will - in addition to covering the basics of IA interpretation - cover the nuts and bolts of interpreting a LC-MS result...

UDT Interpretation: IA and LC-MS

While START-IT interprets immunoassay (IA) automatically, not all clinics will use START-IT. This chapter will not only cover how to interpret the two main types of UDT - IA and the "confirmatory" testing (LC-MS) - i t will also compare and contrast these options through a highly pragmatic, clinical lens...

There are two main methods of UDT:

The ***immunoassay (IA)*** urine drug test, also sometimes called "point-of-care" testing or "presumptive testing", may be conducted in the office or at the lab. It involves collecting a urine sample and then, on-site, dipping a kit with a number of different drug panels. Results are available within less than 10 minutes. While quick and fairly inexpensive (our kits cost $4.50 including shipping for a 5-panel test), there are drawbacks. First of all, IA only detects drugs for those panels used (i.e. it checks for fewer drugs than LC-MS). Some IA panels have significant cross-reactivity which potentially leads to false positives. Some panels have low sensitivity leading to false negatives. Of most clinical relevance, if a patient denies a result seen on an IA test (patient claims it's a false positive or false negative), it is very difficult to act/discuss potential concerns because the test is limited and you cannot always be confident in the result. This is why it is important to know how to apply confirmatory testing and understand its role and limitations.

In contrast, the ***liquid chromatography-mass spectrometry (LC-MS)*** test, also sometimes called "confirmatory testing", is sent away to the lab. LC-MS typically takes 1-2 weeks to process but the time is often worth the wait. It has much higher specificity (in theory, the test should be 100% specific), however there is always room for associated human error labelling or transcribing results. It is also generally more sensitive than IA so it has less false negatives.[1] It can test for innumerable drugs and metabolites, including carfentanyl and "bath salts" (synthetic cathinones). The drawbacks are that in addition to it taking much longer for the results to come back, it is costly to the system. In Ontario, it is OHIP covered but the lab expense alone costs the healthcare system ~$40/test. For completeness sake, you may also hear about gas chromatography-mass spectrometry (GC-MS) for confirmatory testing. As far as the clinician is concerned, the same principles of LC-MS apply to GC-MS.

You can see that there are pros and cons to both types of testing. Recommendations in the literature about how to choose which method of UDT are variable. Argoff *et al.* interviewed a panel of experts who work with UDT and they came to the consensus that confirmatory testing should be used for baseline and future monitoring of addiction risk assessment instead of accepting the lower sensitivity and specificity of IA.[2] Although confirmatory testing is more expensive, if the clinician is uncertain about the results of IA they should be ordering a follow-up confirmatory test anyway, making the initial IA UDT result nearly irrelevant. In fact, there is some evidence that setting up the clinic to have samples go directly to confirmatory testing can reduce turnover time and costs.[3] The 2017 Canadian Guidelines for Opioid Use lean towards using IA as a first line screening modality because it gives immediate results and is inexpensive.[4] When IA results are unexpected then confirmatory testing with GC/LC-MS should be ordered.

Practically speaking, when choosing which UDT method to use (IA and/or LC-MS), it is very difficult if not impossible to act on an IA result alone. You therefore really need some capacity to order LC-MS. The challenge is ordering it in patients in which it is potentially helpful but minimizing ordering in patients which it's not helpful (due to costs to the system). START-IT offers an innovative solution to this problem because it can automatically discern the level of concern with the IA result (although of course it cannot factor in your clinical Gestalt) and make a strength of recommendation for confirmatory testing. For example, if the patient directly disagrees with the result, START-IT recognizes this discrepancy and strongly recommends confirmatory testing. If the result is expected or the patient agrees with an unexpected result, then START-IT advises that confirmatory testing "may be considered" but is not always necessary. Confirmatory testing has advantages even in these scenarios where the patient agrees with the result, because it checks for drugs in addition to those tested for with the IA panels.

Characteristic	Immunoassay	GC/LC-MS
Speed	<10 minutes	1-2 weeks
False Positives	Many instances of cross-reactivity and false positives (i.e. poppy seeds for opioid panels, ranitidine for amphetamine panel, oxycodone for morphine panel, etc.)	Extremely unlikely to have false positives. However, we have had case reports of improper reporting by the lab
False Negatives	Can get false negatives due to tampering, insufficient quantity consumed or metabolic factors	Can detect drugs in the presence of tampering, can detect metabolites at lower levels and can differentiate between parent drugs and their multiple metabolites
Number of metabolites analyzed per sample	Limited to number of panels on device (usually 5), although could use multiple devices/kits	Can test for every metabolite from one sample
Characteristic	~$5/test for the kit, + human resources	~$40.00/test

Let's describe these two different types of UDT in a little more detail, with specific, common examples illustrating key pearls.

IMMUNOASSAY

Basic science: this paragraph is not directly relevant to clinical practice and we would advise that you don't need to know this, however we are also aware that some of you are curious about the basic science so have included it here. IA strips involve chromatography, antibodies and an agent that produces a signal we can detect. In the case of point-of-care IA, the signal that is produced is simply the presence or absence of a coloured strip to let us know if a certain drug or metabolite was in the sample tested. The urine will carry a chemically labelled antibody, by process of chromatography, across the test strip. The chemically labelled antibody will reach an area on the test strip coated with drug-protein conjugates and the antibody will bind to these conjugates. In the absence of any drug the antibodies will bind the conjugates, precipitate the chemical, and the label will become a detectable coloured line on the test strip showing a negative result (the second line). In the presence of drug the antibody sites will be occupied and no detectable line will form showing a positive drug result (a single line for the control).

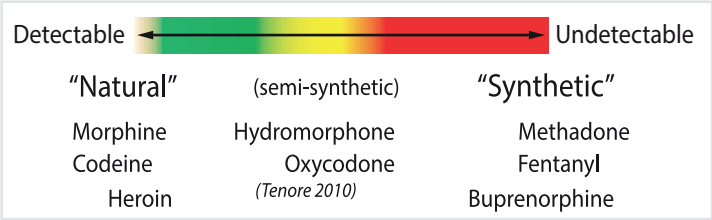
Clinician's Overview:

Now that some of the basic science is out of the way, let's discuss a few caveats for IA. First of all, there is variability depending on the manufacturer (so not all "morphine" panels are created equal). Secondly, patients may tamper with their urine to either hide a drug that's not supposed to be there, or add a drug they're not taking that is supposed to be there (see Appendix C - Anti-tampering Techniques).

The test will generally result as "positive" or "negative", however it very rarely may result as "invalid" (we've had one invalid result in 5 years) in which case it should be repeated immediately. The sensitivity and specificity for a panel, even for the same manufacturer, will have a natural variability depending on the dose and time the drug was taken, as well as individual variations in pharmacokinetics (absorption, distribution, metabolism and excretion). There are enormous lists of agents that have been reported to cause false positives for the IA various panels. Instead of covering these individually, we recommend you consult Moeller et al, 2017[5] or US Pharm. 2016[6] or if using START-IT then it will give you the more common causes of false positives for your specific results.

Now let's go through scenarios and pearls when interpreting the most commonly used panels:

Morphine/Opiate Panel:
The morphine panel, also sometimes called the "opiate" panel (essentially the same thing), is very sensitive for detecting natural opioids. This includes codeine, morphine and (the mildly synthetic) heroin. The more synthetic an opioid, the less detectable. In fact, the fully synthetic opioids like fentanyl, methadone, tramadol and meperidine are not detectable on this panel. The semi-synthetics like oxycodone, hydromorphone and hydrocodone are variably detectable.



Practically, what this means is that if someone is prescribed hydromorphone for example, the morphine/opiate panel has limited utility. If the panel is positive, it suggests the person is taking hydromorphone (although it could be from another opioid). If the panel is negative, it doesn't mean the person is not taking hydromorphone (high chance of false negative). If you are looking for a reliable test for the presence/absence of the more synthetic opioids, then you should consider using specific panels for those drugs (they are commercially available for hydromorphone/hydrocodone, oxycodone, tramadol, methadone, fentanyl, and buprenorphine among others). Practically, you can start to go down the rabbit hole with number of panels so we use the 5 that we consider highest yield in our practice (Morphine, Oxycodone, EDDP (methadone), benzodiazepine and cocaine).

If the patient is prescribed morphine or codeine, then sensitivity of this panel is generally >90%. You will also note that this panel cannot distinguish between morphine/codeine/heroin. If relevant for your patient population, there is a specific IA panel for heroin which tests for a metabolite unique to heroin (6-MAM).

Oxycodone Panel:
The oxycodone panel unfortunately has a sensitivity that has been reported at 75%. This means that up to 25% of people who are actually taking their oxycodone may have a false negative. This of course is very important to know before accusing a patient of not taking his oxycodone just because the IA panel is negative.

Methadone (EDDP) Panel:
EDDP is the main metabolite of methadone. This is one of the most accurate IA panels with sensitivity of 96% and specificity of 99%.

Buprenorphine Panel:
Although studies have varied in the exact numbers, they all show the buprenorphine panel performs with high sensitivity (88-100%) and high specificity (87.5-100%). There have been reports of cross-reactivity with high concentrations of morphine, chloroquine and hydroxychloroquine.[7-11]

Benzodiazepine (BZD) Panel:
This is one of the more challenging panels because there is variability within the BZD class. In general, most BZD panels are designed to detect lipophilic BZD (oxazepam, temazepam, diazepam) and have a low sensitivity for clonazepam and lorazepam. However, even clonazepam and lorazepam are sometimes detected, so if a patient is prescribed lorazepam or clonazepam, this panel is generally not useful (a negative result cannot be acted on, a positive result supports that person took it but is not proof).

Cocaine Panel:
This is likely one of the most helpful panels when it's positive. Specificity is reported as being as high as 100%[12], so if cocaine IA panel is positive it means the person used cocaine. There are no agents known to cause false positives besides coca leaves. That said, sensitivity of this panel is low so it will frequently miss cocaine use.

Amphetamine Panel:
The amphetamine panel is the most difficult to interpret because of the many drugs that have cross-reactivities with this panel with many possibilities for false positives. Methamphetamine will likely be picked up by this panel but MDMA (ecstasy) is often missed and should be detected by an MDMA specific panel. Studies on the performance of amphetamine immunoassays vary greatly depending on the sample population they use because so many other drugs can cause false positives. In general this panel has been shown to have high sensitivities (around 100%) while the specificity can vary greatly (58-99%) depending on the patient population.[13-16]

Fentanyl Panel:
The fentanyl panel may be of increasing importance as more of it is found mixed into street drugs and for monitoring out-patients using fentanyl patches. There are fewer studies demonstrating the performance of fentanyl IA technologies but those that exist show high sensitivities (approx. 100%) and high specificities (86-99%). There has been report of cross reactivity with risperidone and trazodone. Fentanyl analogs like carfentanyl will also cause a cross-reaction but natural opioid analogues will not.[17-19]

Interpreting IA results:
To summarize, there is significant variability between the various IA panels in terms of sensitivity and specificity. Remember that results should be used to complement the rest of the clinical picture, and that with few exceptions IA can have false positives and negatives. First make sure that you know what the test result is suggesting, and if this suggestion is unexpected then consider explanations for a false positive/negative. Strongly consider confirmatory testing followed by an open discussion with the patient. It is very important that you understand the limitations of the test prior to discussing the results with the patient so as to not mismanage based on a misinterpretation or misunderstanding of the limitations of UDT. For more information about how to act on UDT (IA and/or LC-MS), see Chapter 9.

LIQUID CHROMATOGRAPHY-MASS SPECTROMETRY

Basic science: this paragraph is not directly relevant to clinical practice and we would advise that you don't need to know this, however we are also aware that some of you are curious about the basic science so have included it here. Chromatography is the science of separating drugs, metabolites, proteins or other compounds based on their chemical properties. In chromatography you will always have a column with a stationary phase that is designed to retain these compounds in the column and a mobile phase that pushes the compounds out of the column. Based on chemical properties, every different compound will travel through the column at a different speed. In gas chromatography (GC) the stationary phase is a polymer and the mobile phase is a gas heated to extreme temperatures. The drugs or metabolites of interest must be also turned into a gas through extreme heat to be analyzed through gas chromatography. If it is not possible to become a gas the drug or metabolite will need to undertake a chemical derivatization reaction before entering the column. This increases the work to analyze your sample and limits the amount of substances that are possible to analyze. In liquid chromatography (LC) the sample is also placed on a column packed with a polymer but the mobile phase is pumped in at high pressures as a liquid solution. It is possible to analyze over 300 different substances at once using LC. The drugs or metabolites will be detected by a UV detector at the same time as their control would and can be accurately confirmed by tandem mass spectroscopy (MS) to identify the exact molecular weight of the substance leaving the column.[20]

LC-MS Clinician's Overview:
Confirmatory testing is essential when the patient disagrees with the result suggested by presumptive testing (IA), or when you want to check for more drugs than are readily available on your IA panels. The LC-MS results include specific drugs and metabolites in the urine,

and in theory should have a specificity of 100%. If a drug is detected, then the patient took it (or a parent drug). However, that said, we have had several examples of human error where a LC-MS report came back showing a drug was taken, but after adamant refusal by the patient and reinforcement from the rest of the clinical picture, the lab was contacted and there was a reporting error (i.e. the person didn't actually have those drugs in their urine even though the report indicated that he did). The other time where you may get tricked, although not relevant in countries such as Canada where Vick's Nasal inhaler is not available, is that Vick's Nasal inhaler has methamphetamine, however it's the enantiomer of the methamphetamine used in "speed" or crystal meth. The commonly used LC-MS cannot tell the difference. In other words, it might look like the person consumed "speed" when in fact it's simply an over-the-counter nasal inhaler.

One of the more challenging aspects of interpreting LC-MS results is in knowing the numerous breakdown products. For example, codeine is metabolized into numerous other opioids and if you were not aware of this, you may see hydromorphone in someone's urine who is prescribed codeine and falsely assume that he has been taking a non-prescribed opioid.

There are two ways to approach the vast amount of information when interpreting what a LC-MS result means. You could either start with the parent drug that the patient is supposed to be taking and look for the expected metabolite(s) to confirm consumption, or alternatively you could look at metabolites and work backwards to discern what this suggests about patient consumption. In general, it is easiest when looking at a prescribed drug to check for one of more metabolites. And when metabolite(s) show up that are not something you are expecting, you work backwards to determine what substance could cause this result.

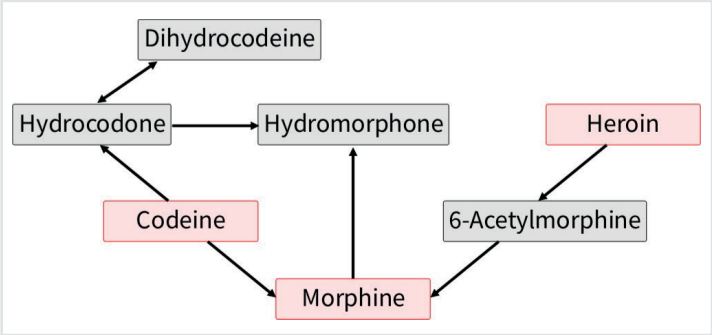
One challenge that came up for us with several patients at our clinic revolved around impurities in prescribed medication. In an ideal world, a patient's "morphine" medicine has 100% pure morphine, however unfortunately that's not the case. As you can see from the table below, numerous opioids have impurities of closely related opioids. So if someone is on a high dose of one of these opioids, that could cause a "false positive" for another opioid on LC-MS

Commercial Active Pharmaceutical Ingredient (API)	Process impurities	Allowable Limit (%)	Typical Observed (%)
Morphine	Codeine	0.5	0.01 - 0.05
Codeine	Morphine	0.15	0.01 - 0.1
Hydrocodone	Codeine	0.15	0 - 0.1
Hydromorphone	Morphine Hydrocodone	0.15 0.1	0 - 0.025 0 - 0.025
Oxycodone	Hydrocodone	1	0.02 - 0.12

Table adapted from Shults, T. MRO Advisory: Critical Pre-Publication Information for MROs on Opiate Interpretations.[21]

Pearls for the more common LC-MS scenarios in clinical practice are described below:

Opiates ("natural" opioids like codeine/morphine and the mildly synthetic heroin):
Codeine is one of the most important opioids to know because it is the most commonly prescribed short-acting opioid in this province[22] and it has so many metabolites that errors in interpretation are easy to make. As you can see below, codeine is broken down into morphine, hydromorphone and hydrocodone - all of whom are prescribable opioids (parent drugs) themselves. So if a patient has taken codeine, you cannot readily determine if he also ingested one of these other drugs. That said, if you see 6-MAM then this means that the person consumed heroin (it's not part of codeine pathway). Another challenge is that poppy seeds actually contain very small amounts of codeine and morphine.[23,24]



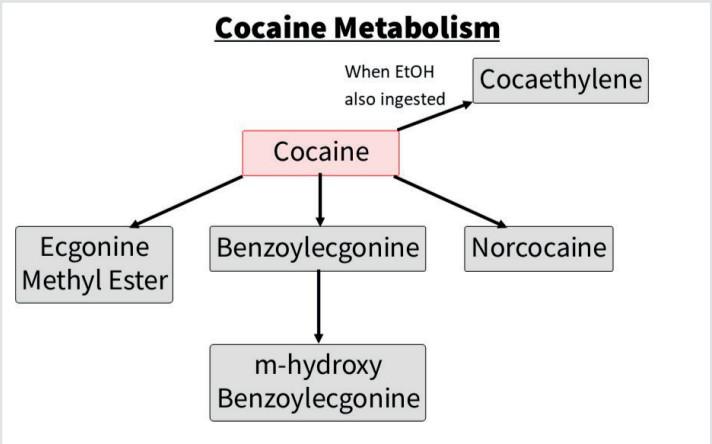
Figured adapted from Pesce et al. (2012)[25]

Likewise, you can see that if someone is taking morphine, then he may also have hydromorphone detected in his urine. While based on metabolism alone you would not expect someone prescribed hydromorphone to have morphine in his urine, or someone prescribed morphine to have codeine, remember from above that there can be impurities in the drug taken that are detectable (particularly at higher doses) and these do not necessarily indicate taking non-prescribed opioids.

Synthetic Opioids:
Contrasted to the opiates ("natural" opioids), the more synthetic opioids have their own metabolic pathways and are generally much simpler to interpret on LC-MS. Below are some examples of semi-synthetic and synthetic opioids, and what you may see on LC-MS:

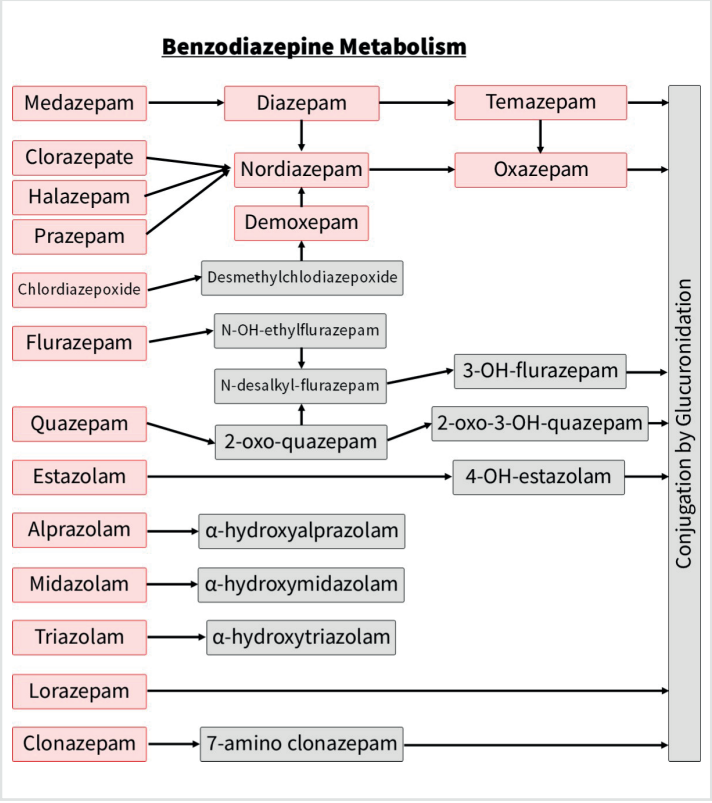
- Oxycodone: Oxycodone, Oxymorphone, Noroxycodone
- Methadone: EDDP, Methadone
- Buprenorphine: Buprenorphine, Norbuprenorphine
- Tramadol: O-desmethyltramadol, N-Desmethyltramadol, tramadol
- Fentanyl: Norfentanyl, Fentanyl

Cocaine:
The parent drug cocaine is rarely detected. The drug that is typically detected to indicate cocaine use is a metabolite of cocaine called benzoylecgonine. This stays in the urine ~3 days, however in heavy users can stay up to 10 days. The other drug commonly detected on LC-MS with cocaine use is levamisole, which is a cutting agent. You may also see cocaethylene which indicates alcohol and cocaine co-ingestion.



Figured adapted from Smolinska-Kempisty, et al. (2017)[26]

Benzodiazepines:
The most challenging benzodiazepines to interpret are, similar to opiates, those with numerous metabolites that themselves can be parent drugs. For example, temazepam and oxazepam in the below metabolism chart:



Figured adapted from Pesce et al. (2012)[25]

Contrasted to diazepam and its metabolites, clonazepam and lorazepam have their own breakdown pathway and so these tend to be simpler to interpret on LC-MS.

Miscellaneous:
A common scenario, even after doing this for many years, is that a metabolite shows up on LC-MS that you have never seen before and doesn't seem to resemble any drug you're familiar with. See case 4b below for an example of how you might navigate through this scenario.

FALSE NEGATIVES

False negatives can occur on both IA and LC-MS. There are several explanations for false negatives: [5,27]

- Dilute urine (excess fluid intake, diuretic use, pediatric sample)
- Infrequent drug use
- Prolonged time since last use (detection windows vary greatly between drugs, and significant variability even within the same drug)
- Recent ingestion
- Insufficient quantity ingested
- Metabolic factors
- Inappropriate test used
- Elevated urine lactate
- Tampering

For quick UDT interpretation from your smartphone, we would highly recommend our free app "UrInterpret". In addition to there being sections describing both HARMS and START-IT, there is a section with Cases where you can practice with realistic, common scenarios. The section that we use the most ourselves is called "Quick UDT". It is a user-friendly way of getting quick answers to your UDT interpretation questions, such as,

For IA,

- *The morphine panel is positive, what drugs may have caused this?* Or conversely...
- *My patient is prescribed hydromorphone, which panels would I expect to be positive?*

For LC-MS,

- *LC-MS detected hydromorphone, which drugs may have caused this?* Or conversely...
- *My patient is prescribed morphine, what metabolites may I see on LC-MS?*

Visit our website www.harmsprogram.ca/urinterpret to see more about how it works.

Cases

Case 1

a. Mr Smith is prescribed long-acting codeine for chronic back pain at 100mg BID. He denies any other drugs. His IA panels come back positive for "morphine", but negative for BZD, cocaine, EDDP (methadone) and oxycodone. Is this expected? *Yes, codeine is metabolized into morphine and should be detected on morphine IA panel. False negatives are of course still possible and more likely with lower infrequent doses, so if it was negative it does not prove that he is not taking his codeine. In that case, await LC-MS results.*

b. Your clinic sends his urine off for confirmatory testing and it comes back showing morphine, codeine, norcodeine, and norhydrocodone. Is this expected or unexpected? *Expected - remember that codeine has numerous metabolites. If you're not sure, look it up (our UDT app UrInterpret has a user-friendly way to quickly see metabolites for any drug).*

Case 2

a. Mr. Green is prescribed long-acting oxycodone 40mg BID for chronic knee pain. He denies any other drugs. His IA panels come back positive for cocaine but negative for oxycodone, BZD and EDDP (methadone). i) How sure are you that he took cocaine? *Very concerned, specificity is reported as being as high as 100%.* How sure are you that he *didn't* take his oxycodone? *Not completely sure, remember that sensitivity of oxycodone panel is reported at 75% (although significant variability). However this patient is on a higher dose of oxycodone so false negative is less likely. Definitely need to send this result for confirmatory testing.*

b. Confirmatory testing comes back showing benzoylecgonine, levamisole, cocaethylene, methamphetamines, amphetamines. i) Which metabolites here are related to cocaine? *Benzoylecgonine is the main metabolite of cocaine, levamisole is a cutting agent used in cocaine, and cocaethylene is a metabolite of cocaine when consumed with alcohol.* ii) How concerned are you now that patient is not taking prescribed oxycodone? *Very concerned, absence of oxycodone in his urine - especially with a dose as high as 80mg daily - suggests he is not taking it. The presence of cocaine and methamphetamines, with the absence of the prescribed oxycodone - may suggest (although certainly not prove) that patient is selling/trading his oxycodone to support buying his drug(s) of choice.*

Case 3

a. You inherit Mrs. Brown into your practice who is prescribed clonazepam 0.5mg BID as well as hydromorphone long-acting 6mg BID. You decide to do a baseline UDT for risk stratification and IA comes back positive on the "morphine" panel, but negative for BZD, cocaine, EDDP (methadone) and oxycodone. How concerned are you that patient is taking a non-prescribed opioid? *Not at all concerned, hydromorphone as a semi-synthetic is variably detectable on the morphine panel and so the positive morphine is explained by the hydromorphone. Likewise, if the morphine panel was negative this would not suggest that patient isn't taking it (this would likely be a false negative).* How concerned are you that patient is not taking the prescribed clonazepam? *Not at all concerned, sensitivity of BZD panel for clonazepam (and lorazepam) is low so false negatives are common.*

b. LC-MS comes back positive for hydromorphone, 6-acetylmorphine (sometimes reported as 6-monoacetylmorphine or 6-MAM), clonazepam, amino-clonazepam. How concerned are you about the presence of 6-MAM? *Very concerned, this indicates that patient consumed heroin and warrants further discussion with patient in a non-judgmental, supportive manner.*

Case 4

You inherit Mrs. White who is prescribed diazepam 10mg BID and long-acting tramadol. Her IA result is positive for BZD but negative for morphine, oxycodone, EDDP (methadone) and cocaine. i) How concerned are you that she is not taking her tramadol? *Not at all concerned - tramadol is a synthetic opioid and it is not detectable on the morphine panel. Would you have been concerned if her BZD panel was negative? Yes, although false negatives for BZD panel are possible, diazepam should be detected (contrasted to clonazepam and lorazepam which have high rates of false negatives).*

a. LC-MS comes back showing nordiazepam, oxazepam, temazepam, tramadol, chlorpheniramine, pseudoephedrine, diphenhydramine, dextromethorphan and methcathinone. How concerned are you about the numerous benzodiazepines detected? *Not at all concerned - remember that these are metabolites of diazepam.* What do you do about the "methcathinone"? *This is a real example to illustrate how to address some of the challenging scenarios. After years of applying UDT, we had never heard of "methcathinone". A quick google search suggests it is a recreational drug that acts as a potent stimulant with euphoric effects. This seemed very unusual for the patient, so the lab clinical biochemist was contacted by email who confirmed that methcathinone can be seen as a "pharmaceutical impurity of some pseudoephedrine and ephedrine preparations". In other words, OTC cough and cold medications can cause this. This is a good time to consider using our UrInterpret App If not sure about what a result means, or if it seems unusual for the patient, contact your clinical biochemist - they are very helpful. Try to have the discussion with the patient after you know what the result implies.*

Case 5

a. Mr. Red is stratified as low-risk and stable long-term on four T#3 per day (120 dispensed q30d) for rheumatoid arthritis. He is called for random UDT and his IA comes back positive on the morphine and BZD panels. Cocaine, EDDP and Oxycodone panels are all negative. He denies using BZD. What do you do? *Waiting for the confirmatory testing results is the first step. Result is definitely not so concerning that you need to act prior to LC-MS results coming back. If a BZD shows up on LC-MS then almost certainly the patient consumed one. Even if that was the case, you would still have to make sure that it wasn't taken as part of a procedure that the patient forgot about (dental, surgical, ER, etc.). In real-life, this patient's LC-MS came back showing no BZD. After review of potential false positives, what likely happened in this scenario was that the patient's sertraline caused a false positive for the BZD panel.*

Chapter Pearls

- Numerous pearls highlighted above for the common UDT results/scenarios.
- To order LC-MS, write "Broad spectrum urine tox screen" on the requisition. If you write "urine tox screen" then the lab often by default will process a "urine drug of abuse screen" which is a lab-based IA test, and you will therefore not have a confirmatory result.
- It is critical to interpret the UDT within the clinical context, and ideally you have confirmed the limitations (including potential false positives and negatives) prior to discussing with the patient. If you are not sure about what a result means, or if it seems surprising for a particular patient, then seek expert consultation (on LC-MS - this often means consulting the lab clinical biochemist).
- Your clinic needs a method for sending the result for confirmatory testing. You can rarely act on the IA result alone. START-IT offers a helpful way of stratifying the level of concern with a result and guiding which samples to send for confirmatory testing.

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Now that we've covered how to interpret UDT results, let's look at how we might apply those results to the management of real patients...

Managing UDT Results

Now that we have an understanding of how to interpret UDT results, it is important to understand how to act on the full spectrum of concerns. . .

UDT results will fall along a spectrum ranging from expected, to mild aberrancy, to major aberrancy. There is also an axis for level of certainty in the result - from low level of certainty (high potential for false positive or false negative) to high level of certainty. This wide range of results must then be applied to a wide range of patients who will have innumerable other unique factors that contribute to the overall clinical Gestalt. You can see that there are an infinite number of scenarios so memorizing approaches without a deeper understanding of what we are doing is not possible. Understanding the big picture when applying UDT results is critical. UDT is meant to contribute to the clinical Gestalt, as we weigh the risks and benefits of prescribing opioids. It is not meant to be a replacement for clinical Gestalt.

By understanding the important factors that suggest someone is being helped or harmed by opioids, we can make more informed decisions about if/how we prescribe them.

The decision about if and how to prescribe opioids essentially comes down to weighing risks against benefits. The Clinical Gestalt will fall along a spectrum ranging from Benefits>>Risks, to Risks>>Benefits. When we first start someone in HARMS, we are estimating which scale is most representative of this patient. When new information such as UDT results come in, the scales may tip and the risk category changes. This chapter will primarily cover what factors we should consider when assessing where a patient falls and how we should adjust the balance based on new information (such as UDT results).

Benefits>>Risks
Low Risk - infrequent UDT, longer dispensing intervals.

Benefits>Risks
Medium Risk - infrequent UDT, shorter dispensing intervals.

Benefits~ Risks
High risk - consider alternative treatment options - if continuing to prescribe opioids then very short intervals, frequent UDT.

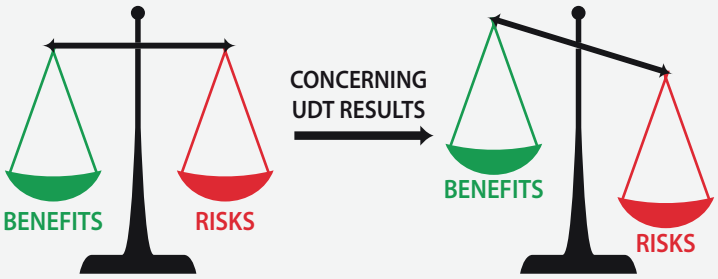
Risks>Benefits
Patient should probably have opioids tapered and stopped (unless opioid addiction is identified in which case you would rotate to OAT).

However, if you decide to keep prescribing opioids for "pain" in this patient then you may consider a hybrid between opioids for pain and opioids for addiction in which you have daily dispensing and frequent UDT (we call this the "structured" stream).

The only challenge is that if truly treating pain then you generally would be using TID-QID dosing, whereas OAT is typically OD dosing. While both would have daily observed dosing at the pharmacy, the "pain" patient would typically get take-home doses (or multiple observed doses at the pharmacy). You will have to use clinical judgement about take-home doses or consider using 24hr-release morphine formulations if comfortable.

Risks>>Benefits
Taper and stop (or if OUD is identified, rotate on to OAT).

To illustrate how the scale will tip based on new information, imagine a patient that is high risk has new and concerning UDT results. You can see how the risks side becomes heavier, and now our overall risk/benefit assessment has shifted. We must therefore adapt our prescribing/monitoring approach to this new information, and evolving risk category.



So if the decision of if/how to prescribe opioids - and how to adapt to new information - comes down to weighing the risks/benefits, what types of factors contribute towards this risk/benefit balance?

Markers of Benefit from opioids may include:

- Function
  - Social stability (work, relationships, housing, etc)
  - Engagement in hobbies/activities
  - Day-to-day function (7 categories within BPI[1])
    - General activity
    - Mood
    - Walking ability
    - Normal work (including work outside the home and housework)
    - Relations with other people
    - Sleep
    - Enjoyment of life
- Pain - this is inherently subjective so unfortunately has limitations, however it should be considered

Markers of Risk from opioids may include:

- Signs of opioid use disorder
- Side effects of opioids
- Poor pain diagnosis
- UDT result
- Risk Factors for Opioid misuse/abuse (see Chapter 2)
  - History of substance use disorder
  - History of mental health diagnosis
  - Opioid prescription characteristics
    - Higher doses (> 90mg morphine equivalent/day recommended as one watchful dose[2])
  - Demographic factors:
    - Younger age
    - Male sex
  - Family history of substance use disorder
  - History of sexual abuse in females
- Red Flag Behaviours (See Appendix 5)
  - Selling prescriptions or prescription forgery
  - Obtaining opioids from nonmedical sources (ie. purchasing street drugs, stealing/borrowing from family/friends)
  - Double doctoring (seeking medications from other clinicians or ER)
  - Altering oral formulations (injecting, biting or crushing)
  - Concurrent abuse of alcohol or illicit drugs
  - Multiple dose escalations or other noncompliance
  - Early refills
  - Multiple episodes of prescription "losses"
  - Deteriorating function (ie. work, family, socially)
  - Resistance to therapy changes despite clear evidence of side effects (adverse physical or psychological)

We use our clinical judgement to essentially plop these weights (and any others you can think of that aren't listed here) onto a scale as we form a clinical Gestalt.

For example, if someone has significant benefits from opioids and since starting them is now working for the first time in a decade, then this is a "heavy" weight towards the benefits side. Even if that person has a history of substance use disorder (a weight on the risk side), assuming other factors are non-contributory, benefits outweigh risks at this point in time. Note that a formalized scoring system is not used here. We use our clinical judgement.

Given that the risk/benefit balance can fall along a spectrum, it is important that our approach to prescribing and monitoring opioids can match this spectrum. To put it explicitly, it's not a matter of simply deciding to prescribe or discontinue the opioid. There are middle-ground options where we can tighten control without necessarily discontinuing the medication. For example, with a higher risk patient in whom benefits still may outweigh risks, short dispensing interval and more frequent UDT leads to tighter control. With lower risk patients, longer intervals and less frequent UDT. This is all captured in the HARMS Program Risk Ladder. The Risk Ladder guides not only how to tailor UDT frequency to patient's initial estimated risk, but perhaps more importantly, it guides how to adapt our monitoring/prescribing to the full spectrum of UDT results.

While the Risk Ladder was designed to guide how we adapt our prescribing/monitoring to UDT results, the same principles discussed here can be applied to any factor that shifts the risk/benefit balance. For example, if someone has decreasing social stability or recurrent early refills, then that would add a weight to the "risk" side of the scale and may be a reason to move up the Risk Ladder. If someone has a new stable relationship and depression is in remission (benefits have gone up, and risks have gone down), then that may be reason to move someone down the ladder.

Now that we've covered the "big picture", let's look specifically at how we respond to UDT results. This is one of the main obstacles to applying UDT in clinical practice - we often struggle with how to act on the results. There are minor concerns on UDT and/or likelihoods of a false positive/negative, and at the other end of the spectrum are major concerns that are essentially 100% accurate (a drug is detected on LC-MS that is not a metabolite, or potential pharmaceutical contaminant, of a prescribed medication). It is for this reason - UDT results having a spectrum of concern from minor to major - that our response to UDT results should also fall along a spectrum. This is where the HARMS Program Risk Ladder becomes particularly valuable. To reiterate - while it is used to guide how we prescribe and monitor based on a patient's initial risk estimate, it's main value comes in guiding how we respond to UDT results. An additional benefit is that it can be applied to not only the UDT results, but any clinical concern (new behavioural observations, social instability, etc.)

The general aim of the Risk Ladder is to balance safety and patient convenience. If someone is low risk, then there is no need to inconvenience them through frequent UDT and short dispensing intervals (these interventions would have little to no safety benefits for someone who is low risk). Likewise, if someone is higher risk, then these increased safety concerns justify tighter control (at the expense of patient convenience) with more frequent monitoring (UDT), and smaller amounts of opioid dispensed at a time. Remember that balance is central to the HARMS Program. In the case of the Risk Ladder, we are trying to balance patient safety and convenience.

The Risk Ladder assumes that everyone - even the lowest risk patient - has some risk and therefore is subjected to universal precautions with UDT. If the universal monitoring with UDT detects a concern, then control is tightened. The process is dynamic - with initial risk estimate guiding the frequency of monitoring, and monitoring results in-turn guiding risk level, then refined risk level adjusting further monitoring frequency, and so on in an iterative process. A minor/soft concern may lead to increased monitoring, and if this concern grows then monitoring and prescribing will get tighter and tighter. This iterative process aims to hone in on the best estimate of risk/benefit balance.

If the clinical Gestalt (from UDT or otherwise) means that the risk category should be shifted, then - in addition to discussing with the patient - the physician should notify the clinical administrator who maintains the master list so that it can be updated.

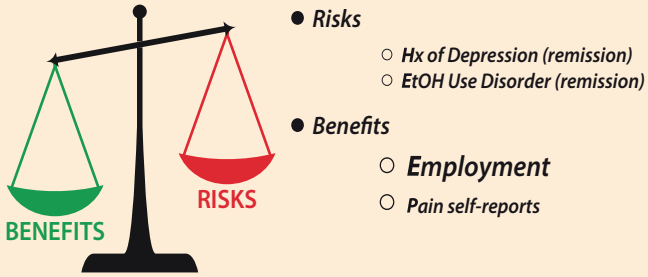
Cases

Case 1

56 year old male labourer on oxycodone/acetaminophen 120 tabs q30d for knee pain for over five years. He presents saying his knee pain is worse with a change in his job, and he's going to be out of his Percocet tomorrow (9 days early). This is his first early refill request and you have no other concerns. What should you do? *Although this result does not include a UDT result, it is helpful to think about movement on the ladder in response to any clinical concern (UDT or otherwise). In this case, a first early-refill request with a good explanation, in someone who otherwise is clinically stable, would likely be considered a "minor" concern. Depending on your Gestalt, and your practice style, there are likely 3 options for this patient: i) the most "severe" might be to consider moving him up one rung (ie: shorten his interval). It likely isn't justified moving him up more than one rung unless there are other concerns. ii) intermediate concern - if you think the concern is so minor that no movement on the ladder is justified, but "something" should be done to avoid it happening again - consider a middle-ground of a "notice". You can think of this like a "strike", although that word may be too pejorative. You may say something to the effect of: "We can do an early refill this time. However I'm going to put a note on your file and if you have another early refill request then we will have to shorten your interval." We've found this very effective - it's serving as going up half a rung. iii) If you are not at all concerned, then you may oblige his request with no movement on the ladder and no "notice", but be careful if this becomes recurrent and re-evaluate if more requests come in.*

Case 2

a. 35 year old female has been transferred to your practice on oxycodone/acetaminophen 4 tabs/day. She has a 2 year history of opioid use for back pain since a motor vehicle accident. She has a history of depression and alcohol use disorder (in sustained remission) and has been working as a personal support worker at the local hospital for the last year. How would you risk stratify her initially based on the limited information you have? *While you would almost certainly do a complete history and physical, and review old records, and consider a baseline UDT, for the sake of this case let's say that you stratify her as Medium Risk (Level 3) because she has concerns on history (Depression, EtOH Use Disorder) but appears to be doing well right now (working, abstinent of EtOH).*



b. She goes on to have one early refill with an episode of increased pain. She begins taking increased time off of work, and no-showed for her UDT. She finally presents to the office for a UDT and the IA is positive for cocaine and oxycodone. She also acknowledges that she has relapsed with her EtOH Use Disorder. What do you do? *This is a complicated scenario but highly realistic. Note that there are numerous factors here contributing to her risk/benefit balance. Again, memorization of cases is not helpful - what is helpful is to think of the big picture. If we were to plot her story on a risk/benefit scale, this is what is happening:*

- *Risks*
  - ***EtoH Use Disorder (active)***
  - *Hx of depression*
  - *Non-compliance with clinic appointments*
  - *Early refills*
  - *Job instability*
  - ***Cocaine use on UDT***
- *Benefits*
  - *Pain self-reports*

Note how we can apply this approach to any patient, with any constellation of symptoms/history/UDT results, etc. In this case, her risk has most certainly changed and you will have to use your clinical judgement to decide if you continue to prescribe opioids long-term (vs tapering and stopping), and if so, how tightly you would like to prescribe and monitor. An open, non-judgemental discussion with the patient is always crucial. As a side note, remember that cocaine on IA has ~100% specificity so the risk of a false positive is essentially zero. You therefore could discuss prior to the LC-MS result coming back. The concerns identified in this patient likely justify going at least to Level 4, if not 5, or even to taper and stop opioid medications.

Case 3

45 year old male with chronic pain and a past history of EtOH Use DIsorder. He was initially a risk Level 3 due to his history but has been on a stable dose of morphine for the past 2.5 years, working regularly at a retail store, and in a stable relationship. He has regularly presented for UDT with negative results and has developed trust with his primary care provider with moves down the risk ladder to Level 1 (longer intervals between dispensing and less frequent UDT).

Remember that every situation can be approached by thinking about the risks and benefits, and how much weight they carry. Again, memorization of cases is not helpful - what is helpful is to think of the big picture. If we were to plot his story on a risk/benefit scale, this is what is happening:

- *Risks*
  - *Hx of EtOH Use Disorder*
- *Benefits*
  - ***Stable Employment***
  - ***Stable Relationship***
  - *Absence of behavioural concerns*

Today's IA UDT was positive for morphine and oxycodone. Patient self-reported the oxycodone and says that his pain was so bad on the weekend that he got some off of a friend. What should you do?

- ***Risks***
  - *Hx of EtOH Use Disorder*
  - *Aberrant UDT Result*
- ***Benefits***
  - ***Large weight for working***
  - ***Large weight for stable relationship***

Note that this is likely not reason to taper and stop his medications, but there has been a shift in the risk/benefit balance and you should probably increase his Risk Level (2 or 3 would seem appropriate, at your discretion and taking into account his honesty, your relationship with him, etc.). If he goes on to lose his job, and his stable relationship, then you can see how the scale will continue to tilt and your approach will have to continue to adapt to the new information. Remember that all we are doing is incorporating the information we have (UDT and innumerable others that constitute the clinical picture of the person) into a risk/benefit assessment and prescribing and monitoring according to that assessment.

Chapter Pearls

- UDT is only one piece of the clinical picture. It should complement the rest of the clinical picture when making decisions about how to act on results. Any piece of i nformation that contributes to your overall risk/benefit assessment can be used.
- Consider using a clinical approach like the HARMS Program Risk Ladder when acting on UDT results. If a UDT result is concerning - or there are behaviour concerns such as recurrent early refills, lost prescriptions etc. - then movement up the ladder should be in proportion to degree of concern. A high degree of concern means significant movement up the ladder (if not off of the ladder completely), whereas a minor concern may mean going up one rung.

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With the core aspects of the HARMS Program covered, the appendices go into more depth about various areas that may warrant further clarification. . .

Appendix A: HARMS Program Implementation

If you are interested in adopting HARMS, then it is very important you review this section. We expect others can learn from our implementation process. There are some important factors to consider prior to implementing HARMS that - from our first-hand experience - will make your lives easier...

Consideration prior to implementation

There are numerous elements you should consider preparing for prior to implementing a UDT system such as HARMS. The key here is that you will ideally have everyone at the clinic on board, and by preparing appropriately you can avoid some of the challenges that we faced with implementation of our system.

Physician education

1) Theory about why UDT is useful - using parts of this manual (Chapter 9 in particular), or one of our online videos (http://harmsprogram.ca/harms-program/) is a good place to start.

2) UDT Interpretation: In addition to getting physicians behind the idea that UDT is useful and - in a structure such as HARMS - not too onerous, it is important to inform physicians that we are, on the whole, not adept at UDT interpretation. Understanding this limitation will hopefully prevent misinterpretation of UDTs, and subsequent mismanagement decisions. Reviewing Chapter 8 of this manual, or even simply by using START-IT, is a good place to start to avoid misinterpretation errors.

3) Myths: there are a few physician cognitive errors that are important to dispel. The absence of observing behavioural concerns is not enough to conclusively say that the patient is not being harmed by opioids (hence why we recommend UDT with everyone prescribed opioids for CNCP). Secondly, it is important that physicians understand that the goal of UDT is not to punish patients. The goal is simply to inform the risk/benefit balance and guide if/how we may prescribe opioids.

Administrator education

The goal here is to educate administrators on their role within the HARMS Program. That really comes down to taking the burden of the UDT system off of physicians as much as possible, as we try and identify who might be harmed by opioid medications. There are chapters within the manual, identified at the top with the administrator symbol, that are particularly relevant for the administrators. Also of importance, we are not trying to "catch" patients. If the staff has a positive non-judgmental attitude, then this will filter down to the patient experience. We would strongly encourage discussion/roll-out of the program at a clinic staff meeting(s) so that everyone is informed and can ask questions, etc.

Patient education

It is important that patients are aware of the program and why it's being done. Once again, there are likely to be misconceptions. UDT often takes on punitive connotations and patients may initially feel as though it is inappropriate. At the same time, everyone has heard about the opioid crisis and by describing it as a universal precaution to do our part with the opioid epidemic, there should be little push-back. While methods for patient education in a small town such as ours is likely different from larger communities, you may consider placing brochures around the office (link to our brochure), and secondary methods include the previous topics of ensuring that clinic medical staff, and non-medical staff, are educated on how the program works and why it is being done.

Decisions around UDT conduction:

UDT Clinics

We recommend creating a few "UDT clinics" per week, where patients are booked sequentially in blocks, as opposed to booking them sporadically throughout the week. This is for several reasons: if you are using any anti-tampering measures in the bathroom then you only have to set it up twice per week; if you have a part-time staff member conducting the UDT then this staff member can do all the UDT in these blocks, as opposed to either having him/her available throughout the week and/or relying on healthcare providers like nurses.

We book each appointment for 20 minutes. We also allow drop-ins (most relevant for the population with addiction). Consider holding UDT clinics on Tuesday and Thursday. Monday would be an inconvenient time for a clinic because you would have to notify patients on the Friday before which gives 3 days lead-time, and Friday there may be issues with transport to the lab or holidays.

Frequency of UDT Clinics

The vast majority of UDT at our clinic are for opioid agonist treatment monitoring in addiction. Even if your clinic has 300 patients in the HARMS Program for CNCP and they average 2 UDT per year (medium risk), this is still only 12 UDT per week which could be booked in a single 4-hr clinic.

Choosing a method for UDT (IA and/or LC-MS)

A UDT can be provided either in clinic, or at the lab. In our Family Health Team, we prefer that UDTs are provided at the clinic and then as indicated we may send the sample to the lab for "confirmatory" testing. However, we do allow patients that have work conflicts or otherwise cannot attend an appointment to provide a sample directly to the lab. If your clinic has the capacity to conduct UDT on-site (staffing, washroom, supplies, etc.), then we would recommend it over providing the sample at the lab. On-site testing allows for application of START-IT and all of its potential benefits for IA (self-report, automated interpretation, recommendations about confirmatory testing, etc.), as well as anti-tampering techniques (if your clinic chooses to use these). As discussed further below, your clinic may even consider just conducting confirmatory testing and skipping IA altogether in which case really the only potential advantage to providing at the clinic is that you have more control over how the sample was provided. We are aware of labs giving the patient a urine specimen container to go home and asking them to bring it back, certainly making it easier to tamper.

If your clinic does not have the capacity to do UDT on-site, then you may still apply the HARMS Program but you would be reliant on using the lab instead. In this case, a requisition would be given to the patient (or faxed directly to the lab) typically for a "broad spectrum urine tox screen" (confirmatory testing with LC-MS). If so-desired, you could order a "urine tox screen" or "drug of abuse screen" (these both indicate IA) instead of, or in addition to, LC-MS.

Choosing IA Panels

There are a number of factors when deciding about which IA panels to use at your clinic. If you want the best "bang for your buck" you want to use panels that capture commonly prescribed drugs, as well as those that are commonly abused in your region. Manufacturers of IA panels can often make whatever combination of panels you want. We use a standard 5-panel with Morphine ("opiates"), Oxycodone, EDDP (methadone), Benzodiazepines, and cocaine. Note that we do not use fentanyl panels because fentanyl is not commonly abused here, and we don't use methamphetamine panels because of false positives. These are personal decisions however. You also have the option of buying a kit that actually has the panels built directly into the cup, anti-tampering built-in (Creatinine/specific gravity/pH) and innumerable other options/combinations.

START-IT considerations

We would recommend using START-IT to simplify the whole UDT process. That said, there are pros and cons.

- **Pros**
  - Saves ++ time
  - Avoids IA interpretation errors
  - Gathers self-report
  - EMR integration (no paper)
  - QI and research capabilities
  - Future capabilities to: administer BPI and treatment agreements, collect consent

- **Cons**
  - Some basic set-up required to optimize it (tablet PC, OCEAN platform)
  - If you don't have one of the EMRs supported on OCEAN (TelusPSS, Acuro, OSCAR) then EMR integration won't work and it will take more time
  - Cost - ~$50/month subscription for OCEAN platform

Anti-tampering methods

As alluded to throughout this manual, choosing which anti-tampering methods to use is not easy. For over 5 years, we have been using blue water in the toilets, taping the faucets, temperature checks, creatinine/specific gravity and pH checks, and despite this we've only had a single urine detected as potentially being tampered (it was too cold). It may not be worth the effort to use all of these methods. In fact, if Dr. RPM were doing this again he wouldn't use any of them.

Consent from patients

We collect consent when initiating the program, but it may be worth collecting consent at each visit. If your clinic decides to do this, then the next version of START-IT will facilitate this through automation of the process.

Staff selection

When we first started the program, we used our RPN appointment slots to conduct the UDT. We then applied for a small grant to hire a part-time, non-medical staff member to conduct the UDT and this was successful. If possible, hiring someone to work part-time doing UDT and facilitating the program would be worthwhile. Either way, you will have to decide: i) Who conducts UDT? ii)Who is designated admin for the program? This second question is important so that physicians have a point-person - this person maintains the master list and communicates with the physicians. Ideally, you can have the same person both conduct the UDT and administer the program. We have our regular booking staff phone the patients to book the appointments.

Chapter Pearls

- Preparation is key - informing all staff members (not just medical) about what the program is and why it is being done is important so that patients are receiving a unified, and non-judgemental message.
- It is ideal to have everyone on board for a program like this to avoid the situation where two patients in the same clinic are treated differently depending on who their physician is.
- Patient education - this too is important. We have found that with education of patients there has been essentially no push-back (although there was some initially, there has been none for years).

Appendix B: Administrative Protocols: Failure to Provide UDT and Unexpected Results

While clinical administration does not need to be familiar with how to interpret UDT, they should be familiar with when to communicate to the prescriber either concerning automated interpretations on START-IT, or repeated failures to provide UDT. This section covers how clinical administration should respond to these concerning scenarios...

Unexpected results:

This section really only applies if you are using START-IT for automated UDT interpretation, or if you have been trained in how to interpret IA results. There are numerous different types of unexpected results, some more concerning than others, but generally speaking you should notify the opioid-prescribing physician of any unexpected result. Possible exceptions to this include those patients that may routinely have unexpected UDT, such as "Level 6" patients prescribed opioids as part of OAT for addictions treatment.

In addition to notifying the prescribing physician, follow the clinic policy around sending for confirmatory testing. At our clinic, we have historically sent all urines to the lab for confirmatory testing. START-IT now makes recommendations about when to send for confirmatory testing as well depending on the level of discordance between patient self-reports and the IA result. Unexpected results in which the patient self-report is discordant with the observed IA result will automatically result in a "strong" recommendation for confirmatory testing.

Equivocal results:

This also only applies if you are using START-IT for automated UDT interpretation, or if you have been trained in how to interpret IA results. There are some UDT results that are not fully unexpected, but not expected either. An example of this would be someone who is prescribed morphine but claims to have not taken it in the last week and UDT is negative for morphine. This result could be simply because the patient is prescribed morphine for intermittent pain flares and hasn't had any recently, or alternatively it could mean that he either took too much of his medication early in his refill or is even diverting the morphine (trading/selling). If you are not sure what to do with the result, we recommend you notify the prescribing physician.

Failure to Provide UDT:

There are numerous reasons that a patient may be selected for UDT but fail to provide one. While the exact reason may be important (on one side of the spectrum is someone who is hospitalized for medical illness so can't make it in, and on the other side is someone who doesn't pick up the phone or return messages, or outright refuses), the bottom line is that someone who fails to provide a urine sample despite numerous attempts (arbitrarily 3 attempts, with variability depending on reasons for failure to provide UDT) has a soft concern that may affect if and how the physician prescribes opioids. The physician needs to know this. Message the physician with an explanation of the attempts that have been made and the patient's response or lack thereof.

It is probably easiest to keep track of each attempt using the "Recall List" tab in the "HARMS Program UDT Randomization" spreadsheet (same one that keeps the master-list and randomizes patients).

Chapter Pearls

- A patient failing to provide a UDT may be concerning. If repeated attempts are made then the prescribing physician should be notified, with as much detail as you have, so that action can be considered.

Appendix C: Anti-tampering Techniques

A UDT is only helpful if it accurately represents what drugs/medications a patient is consuming. While there are limits to testing even if the urine represents what the patient is actually consuming, unfortunately the situation can be further complicated if patients try to "cheat" the test (called "tampering"). This section covers what the most common methods are for tampering with a UDT, as well as some anti-tampering techniques your office may consider using to mitigate these risks...

A urine drug test is only as helpful as it is accurate. An inaccurate UDT however is not only unhelpful, but potentially very harmful if we put too much stock in the result.

While most of this manual has focused on what a result implies about the urine tested, we haven't spent much time discussing whether that urine is truly representative of the urine that patient actually produced under physiological conditions. If a patient tampers with their urine then it may appear to not have drugs that it actually should, or have drugs present that were actually not consumed. Unfortunately, the potential for tampering introduces a whole new element into the challenges of UDT interpretation. Fortunately, it is uncommon. A report in 2015 suggested that 1.5% of the urine samples were adulterated by various means (this was not limited to just patients with pain however, and included patients receiving opioids for addiction treatment).[1]

Unexpected Negative Result

When we get an unexpected negative result by UDT it is easy to first come to the conclusion that the patient is either diverting their medication, not taking what they have been prescribed, or they are tampering with their sample. The following are what should be considered first when receiving unexpected negative results by UDT.

1) Detection Windows and Dose

It is possible to receive a negative result if you are testing the urine outside of the drug's detection window for a particular assay. IA and GC/LC-MS have different detection windows for different drugs which can vary based on patient body mass or metabolic characteristics. If you perform a test too early or too late after ingestion of a drug you may receive a false negative. Also, lower doses of medication will have lower concentrations in the urine and may fall below the detection limits of the test, when compared to higher doses.

2) Metabolic Factors

Sometimes patients have extreme variations in their metabolic profiles. For example, some patients are deficient in cytochrome P450 and will produce low amounts of metabolites. Some patients use other medications that can inhibit metabolism such as through P450 pathways.

3) Appropriate Test Use (i.e. using a sensitive panel for the drug of interest)

Make sure you are using the right test for the metabolite you expect to measure. For example the opiate panel can detect oxycodone but only in high levels (opiate panel has low sensitivity for oxycodone). If you want to measure oxycodone compliance then you should use the oxycodone-specific IA panel which has a higher sensitivity. Also, you should wait until confirmatory testing with GC/LC-MS is completed to have increased confidence in a negative result. [2–6]

Drugs that typically require their own IA specific test

Acetaminophen	Oxycodone
Amphetamines	Phencyclidine
Barbiturates	Propoxyphene
Buprenorphine	Tricyclic antidepressants
Benzodiazepines	Marijuana
Cocaine	Tramadol
Cotinine	Synthetic Marijuana (K2)
Fentanyl	Zolpidem
Ketamine	Methylphenidate
Ecstasy (MDMA)	Alcohol
Methamphetamine	Lysergic Acid Diethylamide
Natural opiates (codeine/morphine/heroin)	Hydromorphone
Methadone	

There are three main ways of "cheating" a urine drug test through tampering:

- Dilution
- Addition of adulterants/oxidants
- Urine substitution

Dilution

One of the most common types of deception with respect to UDT is dilution of the sample, accounting for up to 60% of sample tamperings.[1,7] Dilution is usually as simple as adding tap water or toilet water to the sample while the patient is in the washroom in an attempt to lower the concentrations of substances in the urine sample. A way to detect sample dilution is to measure urine creatinine levels, temperature and the specific gravity. Normally urine creatinine is greater than 20 mg/dL so anything less than this becomes suspicious for dilution. Less than 5 mg/dL is inconsistent with human urine. Dilution via addition of water can also change the urine's temperature to a level inconsistent with human urine. Temperature outside the normal of 32-38°C within 15 minutes of sample production is suspicious of tampering. A specific gravity less than 1.002 is also suspicious for dilution. Although creatinine levels and specific gravity can measure the dilution of urine, always keep in mind that these values can be low due to over hydration, diuretic use, low body mass or kidney diseases that cause renal tubular dysfunction.[2–4,6]

Addition of Adulterant or Oxidant

The addition of chemicals such as household cleaners, special chemicals designed to interfere with the drug assays by masking metabolites, or shavings of the drug being tested to produce a false positive, can all be ways patients may tamper with their urine samples. These account for about 28% of tamperings.[1,7] There are several commercial adulterants and oxidants such as glutaraldehyde, sodium nitrite, potassium nitrite, pyridinium chlorochromate, peroxide and peroxidase. Common household adulterants include bleach, liquid drain cleaner, soap, ammonia, hydrogen peroxide, lemon juice, vinegar and eye drops. There are some adulterant and oxidant assays that are designed to detect some of these products in the urine. If you are not testing a urine sample specifically with adulterant assays you can detect tampering by visually inspecting the urine for its normal clear pale yellow colour or by observing long lasting bubbles after shaking which are caused by the addition of soap or other adulterants. The pH of the urine should be between 4.5 and 8.0 with values outside this range indicating suspicion for contamination. The specific gravity should be greater than 1.002 and less than 1.020. Values outside this range can be caused by sample contamination. Urinary nitrite levels should also be less than 500 ug/mL but can be elevated in the presence of added nitrites. They can also be elevated in urinary tract infections. Addition of anything to the urine may also change its temperature outside the normal of 32-38°C within 15 minutes of sample production.

Tampering through addition of small amounts of a drug into the urine sample by the patient with the intent of producing an artificially positive UDT result is harder to prove and is usually an incidental finding on confirmatory testing. If a drug was added to urine manually by the patient it will usually be present in extremely high concentration and its metabolites will be absent. For example, according to the table below, if buprenorphine or methadone is detected with LC-MS/MS then 97% of the time their metabolites should also be detected. If the parent drug is detected in high amounts without their metabolite, then consider whether the drug could have been added to the urine sample, or the time of ingestion of the drug was extremely recent, or the patient has some metabolic variations such as P450 deficiency or inhibition.[2–4]

Drug	Metabolite	Percent of Times Metabolite Observed (%)
Methamphetamine	Amphetamine	88
Methadone	EDDP	97
Buprenorphin	Norbuprenorphine	97
Fentanyl	Norfentanyl	98
Hydrocodone	Hydromorphone	69
Oxycodone	Oxymorphone	93

Table from Pesce et al. 2012

Urine Substitution

Another form of tampering is through urine sample substitution. This accounts for approximately 14% of tampering cases.[1,7] Patients may use someone else's urine which does not contain any concerning substances, or contains the drug profile required to obtain an expected result during routine UDT. A good indicator of tampering by substitution is the temperature of the sample. The normal initial temperature of urine is 32-38°C. The temperature of the urine should be at least 32-33°C for 15 minutes after the production of the sample. If the urine is lower than this temperature it could be because of a time longer than 15 minutes since production of the sample or dilution of the urine with water or other liquid.[2,3,6]

Anti-tampering Strategies

It is worth noting that anti-tampering strategies fall along a spectrum that could be loosely broken down into being being cheaper and less invasive on one end of the spectrum, to more expensive and more invasive on the other end of the spectrum. Examples are included in the table below, from least invasive to most:

Note that our clinic has employed anti-tampering measures for over five years now, with o ver 1 000 t est results on chronic pain patients as well as patients with opioid use disorder and we have had only one potential case of tampering detected (sample was cold, in a patient prescribe OAT for addiction). Measures that we have used include urine dip for creatinine, pH and specific g ravity; checking urine temperature; and blue water in the toilet. Naturally, we are considering discontinuing anti-tampering methods given the effort it takes however, one could argue that these methods still have utility in that they dissuade tampering.

It is helpful to be reminded that if there is a strong therapeutic relationship - with open discussion, compassion and understanding - the patient's drive to deliberately deceive you should be minimized.

Anti-tampering strategies
Visual inspection of the urine after shaking for colour and persistent bubble formation
Ask patient to remove bulky clothing before producing a sample
Measure urine temperature
Use of IA panels which include analysis of tampering indicators such as creatinine, pH, specific gravity, oxidants or nitrites
Testing of urine with anti-tampering devices which can measure parameters listed above and can specifically detect common adulterants such as bleach, PCC, oxidants and vinegar
Use of coloured water and tampering indicator tape in bathrooms
Remove all chemicals/soaps from the washroom
Disconnect water supply in the bathroom (wash hands outside the bathroom)
Repeated urine sample
Ask patient to put on a gown before going to the washroom
Witnessed urination [1,8]

Cases

Case 1

Jane is a 56 year old female requesting oxycodone for her chronic pain and says she knows only oxycodone helps it. You ask about past or current illicit drug use but she denies any. You ask to obtain a baseline UDT before starting her on a long-term opioid regimen. She is reluctant at first but eventually agrees. She gives a urine sample for IA testing. The IA strip contains indicators for opiates, oxycodone, methadone, cocaine and amphetamines as well as tampering indicators for pH, creatinine and oxidants. Her UDT results come back all negative, the pH is in the correct range, the sample is negative for oxidants but her creatinine measures as extremely low. You ask Jane about any diuretic use or kidney problems and she denies either. You excuse yourself from the room for a moment with the urine sample to shake it and inspect it. It's colour is consistent with normal urine and there is no excessive amount of bubble formation. You also measure the temperature of the sample to be 25°C, much lower than the physiological temperature of human urine and it has been about 10 minutes since Jane produced the sample. Y*ou should be suspicious of dilution of the sample. Further testing of the urine can be done to accurately measure the level of creatinine and specific gravity to determine if it's within the physiological range. A repeat urine sample should also be requested.*

Chapter Pearls

- Tampering is uncommon but very concerning.
- The most common method of tampering is dilution (adding water to the sample, or drinking large amounts of water beforehand to naturally dilute the urine - so that the concentration of an illicit drug consumed gets below the detectability limit).
- In our clinical experience, our anti-tampering methods have only detected a single case of tampering over five years (sample was cold, and it was provided by a patient receiving OAT for addiction - not a HARMS Program patient with CNCP). It is reasonable to consider not employing any anti-tampering techniques.

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Appendix D: Billing UDT

Implementing UDT requires addressing numerous facets, and sustainability of the program and compensation for physician time are important for any program's success. This section covers the billing of UDT...

There is a wide range of variability when billing urine drug testing that depends on numerous factors. This section is written for family physicians in the province of Ontario, however note that there are numerous different payment models and so there is no single approach. Also note that we are in an uncommon payment model called a Rural Northern Physician Group Agreement (RNPGA) where our UDT is considered "in-the-basket" and we receive 5% shadow-billing for what we bill. This has naturally led to us not being experts in the practical application of billing UDT ourselves.

Nevertheless, we have done the homework and at least laid out a review of the OHIP Schedule of Benefits that summarizes the important billing codes for UDT. Highlighted are points 4-8 as they are the most relevant when billing UDT for CNCP. Note that some of the billing codes referenced below - K682 and K683 (OAT), and K623 and K624 (Form 1 and Form 3) - would not be applicable to your CNCP patients.

B. Point of care drug testing	***Fee***
G041 Target drug testing, urine, qualitative or quantitative	*per test 3.70*
G042 Target drug testing, urine, qualitative or quantitative *[**Commentary**: G041 and G042 are tests for a specific drug of abuse.]*	*per test 2.50*
G040 Drugs of abuse screen, urine, must include testing for at least four drugs of abuse	*per test 15.00*
G043 Drugs of abuse screen, urine, must include testing for at least four drugs of abuse *[**Commentary**: Drugs of abuse may include any of the following: alcohol, methadone, methadone metabolite, morphine, a synthetic or semisynthetic opiate, cocaine, benzodiazepines, amphetamines, methamphetamines, cannabinoids, barbiturates or any other drug of abuse.]*	*per test 7.50*
G039 Creatinine	*1.03*

Payment rules:

1. *For the purposes of opioid agonist maintenance treatment, G040, G042, G041 and G043 are only eligible for payment to a physician who has an active general exemption for methadone maintenance treatment or chronic pain treatment with methadone pursuant to Section 56 of the Controlled Drugs and Substances Act 1996.*
2. *G040 and G041 are limited to a maximum of five (5) services per patient (any combination) per month to any physician when K682 or K683 is payable.*
3. *G042 and G043 are limited to a maximum of four (4) services per patient (any combination) per month to any physician when K682 or K683 is payable.*
4. ***Any combination of G040, G041, G042 and G043 is limited to a maximum of three (3) services per patient per month for management of a patient with chronic pain, an addiction, or receiving opioid agonist treatment program where K682 or K683 is not payable in the month for the same patient to any physician.***
5. ***G040, G041, G042 and G043 are not eligible for payment unless K623 or K624 or a consultation, assessment or time– based service involving a direct physical encounter with the patient is payable in the same month to the same physician rendering the G040, G041, G042 or G043 service.***
6. ***G039 is limited to a maximum of two (2) tests per patient per week, any physician.***
7. ***G039 is only eligible for payment when rendered to rule out urine tampering.***
8. ***Only one of G040, G041, G042 or G043 is eligible for payment per urine sample.***

Adapted from OHIP Schedule of Benefits[1]

So practically what this means is that if you do an IA UDT in the office with at least 4 panels, then you would bill a G040 ($15). You must have assessed the patient in that month to be eligible. Maximum of 3 in a given month (for chronic pain patients, this upper limit is only relevant for those that are in your "structured" risk stream as no other patients would be doing even close to this frequency). If you also do anti-tampering with creatinine and/or pH/specific gravity/oxidants, etc. then you would bill a G039 as well.

Chapter Pearls

- Billing for many clinics is an important component of program sustainability.
- Spend the time in early stages inquiring into billing for your unique setting.

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1. Ministry of Health and Long Term Care. Schedule of Benefits: Physician Services Under the Health Insurance Act. November 2018. http://www.health.gov.on.ca/en/pro/programs/ohip/sob/physserv/sob_master20181115.pdf. Accessed June 24, 2019.

Appendix E: Beyond UDT: Other Red Flags for Harm

While UDT is one marker of risk, there are numerous other indicators suggesting that a patient is being harmed, or is at risk of harm, from opioid medications...

While urine drug testing is one of the most objective markers of risk, there are other factors that need to be considered when weighing the risks and benefits. Chapter 9 covers how to act in the clinical context based on the overall balance, with a focus on UDT results. This section will focus on how other observations may contribute to a patient's risk assessment.

It is important to note that not all aberrant behaviours indicate opioid misuse. Some patients may demonstrate aberrant behaviours such as drug hoarding or escalating doses without permission due to other reasons such as inadequate pain control. If pain is adequately treated, these behaviours may subside. It is important to consider alternative explanations for these behaviours within the patient's context.[1]

Commonly observed drug-related aberrant behaviours

More likely predictive of abuse:	Probably less likely predictive of abuse:
• Selling prescription medications or *prescription forgery[1] • *Stealing or "borrowing" medications from others (ie. family and friends)[1] • Injecting oral formulations (or biting or crushing oral formulations[2]) • Obtaining opioids from nonmedical sources (i.e. purchasing street drugs) • Concurrent abuse of alcohol or illicit drugs • Multiple dose escalations or other noncompliance with therapy despite warnings • *Multiple episodes of prescription "losses"[1] • Repeatedly seeking medications from other clinicians or emergency departments (ie. double doctoring) without informing prescribers or after warnings to stop • Signs of deterioration in function (ie. work, family, socially) • Resistance to therapy changes despite clear evidence of side effects (adverse physical or psychological)[1]	• Aggressive complaining about the need for more medication • Drug hoarding during periods of decreased pain • Requesting specific medications • Openly acquiring similar medications from other physicians • Dose escalations or other noncompliance on 1-2 occasions • Unapproved use of the medication to treat other symptoms • Reporting psychic effects not intended by the prescriber • Resistance to a change in therapy associated with "tolerable" adverse effects, with expressions of anxiety related to return of severe symptoms * Those identified as more predictive of opioid misuse by Kaye et al.(2017)[1] Lists adapted from Portenoy (1996).[3] Behaviours were divided based on investigators' beliefs on predictive ability.

Cases

Case 1

Your patient has been escalating their dose twice now and you have other soft concerns for harm. You don't think you have enough to justify tapering and stopping at this point, but you are worried and want to put an end to this pattern of dose escalation. What options do you have? *The real concern here seems to be the pattern of dose escalation. This could be from inadequately treated pain, or alternatively from opioid abuse/misuse. One thing we have found helpful in these particular scenarios is to use the Brief Pain Inventory as a means of measuring the patient's pain and functional impairment (if dose is escalating then typically both scores will be high). If you escalate the dose and then 2 months later the patient comes back wanting another increase, you may apply the BPI again - if the score is the same or worse then naturally it looks like opioids aren't helping. Most of us at the MFHT don't use the BPI otherwise, but once an early habit of dose escalation has been started it's helpful to have this as a means of pointing that out- by the patient's own reports - opioids don't seem to be helping and therefore further escalations are not justified.*
If your clinical Gestalt dictates that a further dose increase is reasonable, then certainly consider moving the person up the risk ladder as these dose escalations are soft concerns for harm and likely tilt your risk/benefit balance

Chapter Pearls

- Be aware of drug-related aberrant behaviours but keep in mind that not all behaviours are indicating drug misuse/abuse and consider alternative explanations within the patients current context.

REFERENCES:

1. Kaye AD, Jones MR, Kaye AM, et al. Prescription Opioid Abuse in Chronic Pain: An Updated Review of Opioid Abuse Predictors and Strategies to Curb Opioid Abuse (Part 2). Pain Physician. 2017;20(2S):S111-S133.
2. Centre for Effective Practice. Opioid Tapering Template. February 2018. https://cep.health/media/uploaded/20180305-Opioid-Tapering-Tool-Fillable.pdf. Accessed August 14, 2019.
3. Portenoy RK. Opioid therapy for chronic nonmalignant pain: a review of the critical issues. J Pain Symptom Manage. 1996;11(4):203-217.

Once red flag behaviours have been identified, the next step is having a discussion with your patient. For guidance on those difficult discussions see the next appendice, F Difficult Discussions with Patients...

Appendix F: Difficult Discussions With Patients

In the last section we outlined some drug-related aberrant behaviours that may lead you to adjusting your patient's risk and even tapering opioids, which may result in a difficult discussion. This section guides how to have difficult discussions with patients when you are addressing an unexpected UDT result or other clinical concern, and/or you would like to make a change to their medication/prescribing/management without the patient being on board...

As this manual has been addressing explicitly and implicitly throughout - the challenge with prescribing opioids for CNCP is that we want to support our patients and minimize their suffering. Most of the time, the patient's goals and our goals are compatible. In the case of addiction and misuse however, the patient may want us to do things that are harmful (keep prescribing a medication that is destroying their life, increase dose and/or quantity, decrease monitoring frequency, switch to different formulation, etc). This discordance naturally brings up challenging conversations. This chapter is meant to be a practical guide on how to handle some of the challenging conversations.

It sounds easy, but the most important thing is to support the patient! This can be very difficult if the patient is upset.

When presented with the scenario of an aberrant UDT or other aberrant behaviours, an appropriate first step would be to consider a differential diagnosis including lab error, miscommunication of provider expectations, inadequate pain control, opioid misuse, addiction or diversion.[1] In the instance where opioid addiction or diversion is highly suspected, the physician will face a difficult discussion with the patient.

Often even the nonjudgmental physician can find themselves with thoughts of whether they can trust their patient, whether their pain is real or to the extent they report it, or whether the patient is drug-seeking or diverting their medication.[1] Being aware of these thoughts is important in avoiding an approach that is punitive and jeopardizes trust along with the patient-physician relationship[1].

A study by Matthias et al.[2] looked at patient and provider views on tapering conversations and identified a key theme as explaining reasons for tapering the medication. Very important to this was providing an individualized explanation to the patient and shifting the conversation away from the current opioid crisis.[2] Highlighting the patient's medical history or unique risks allows for the patient to see applicability to himself/herself.[2] Some patients may fail to see common ground and think the physician does not believe their pain is real or severe. In these instances the physician should empathize with the patient, reinforcing their understanding of the patient's pain and its effect on their function and life.[1] Physicians can further empathize by demonstrating their frustration with a lack of effective medications for the treatment of pain. This can in-turn lead to the discussion of alternative options for treating pain and reinforces the physician's commitment to treating pain.[1] Reassurance that patients would not be abandoned during tapering was another key theme that emerged from Matthias et al..[2]

One approach to the conversation may be to frame the conversation around the benefits and risks of opioid therapy. By informing the patient that the observations are alarming for signs of harm, which now outweigh the benefits of opioid therapy, it avoids the connotation of blaming the patient. Further, by reinforcing the notion that addiction is a possible side effect of opioid use just as others such as constipation or sedation, it allows the physician to blame the medication or treatment rather than inferring fault or stigma on the patient. By expressing concern for the patient's well-being, it can even strengthen the patient-physician relationship.[1]

Some physicians may find themselves using a bargaining technique with their patients, where they negotiate future steps, however some literature[1] suggests this strategy involves the patient and provider being adversary and having opposite goals versus working towards a common

goal with shared decision making. An alternative approach involves providing patients with options. Matthias et al.[2] found that patients and primary care providers had a desire for patients to be given options regarding tapering plans. When the physician provided options for the patient, such as options whether to change dose versus frequency, the patient had some control over the process and it resulted in a process of collaboration.[2]

Another strategy may include use of the HARMS Program and guidelines as "pushback". The idea that "it's not me, it's the program and expectations" is a helpful way to both maintain rapport with the patient (anger can be directed towards the "faceless" program or guideline), and to make sure that the point of contention (concerns about safety) are being addressed effectively. One reason that we built the HARMS program to be applied to everyone at our clinic prescribed opioids for CNCP is so that UDT wouldn't be a matter of physician mistrust. We wanted to make it as objective as possible. It's not that my physician doesn't trust me or is a "bad guy", but rather the program is universal and everyone prescribed opioids for CNCP is subjected to it. Reinforcing the idea that the HARMS Program UDT is a universal tool to identify harms of the medication, rather than a sign of mistrust, allows the provider to maintain the physician patient relationship.[1]

A few lines that we found helpful during discussions with the patient, include:

- "I'm not going to do something that looks like it is harmful to you"
- (if you have BPIs showing that pain and function are not improving despite dose escalations) "I see that you are asking for a higher dose, but you have showed me that increasing your dose is not helping, in fact it is making things worse. This is not uncommon with opioids, they've even coined a name for it (opioid-induced hyperalgesia) and further dose escalations will only make things worse..."

Chapter Pearls

- Shifting patient's anger towards the opioid medication, or the program or guideline, can be a helpful way to maintain therapeutic alliance when making difficult decisions. If referencing guidelines, be wary of appearing too impersonal.
- Consider giving the patient a few options (within your comfort limits) about how they taper, for example changing the dose first, or the frequency.

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2. Matthias MS, Johnson NL, Shields CG, et al. "I'm Not Gonna Pull the Rug out From Under You": Patient-Provider Communication About Opioid Tapering. J Pain Off J Am Pain Soc. 2017;18(11):1365-1373. doi:10.1016/j.jpain.2017.06.008

Appendix G: Opioid Use Disorder

While diagnosing Opioid Use Disorder and getting the patient on-board with new treatment strategies can be one of the most challenging tasks with opioids in CNCP, it is important to familiarize yourself with the steps following diagnosis...

Opioid use disorder (OUD) is the DSM-V diagnosis for opioid addiction. There are numerous technical elements that we could cover (specific criteria including whether OUD is mild/moderate/severe, previous terminology that is still used like Opioid Dependence and Opioid Abuse, etc.), however instead of "reinventing the wheel", this section will simply cite other references for the more technical components of OUD. The material here will focus on some of the practical elements of how to help these patients suffering with addiction. Specifically, it addresses those patients originally seen for "chronic pain" who are subsequently identified as having challenges with addiction.

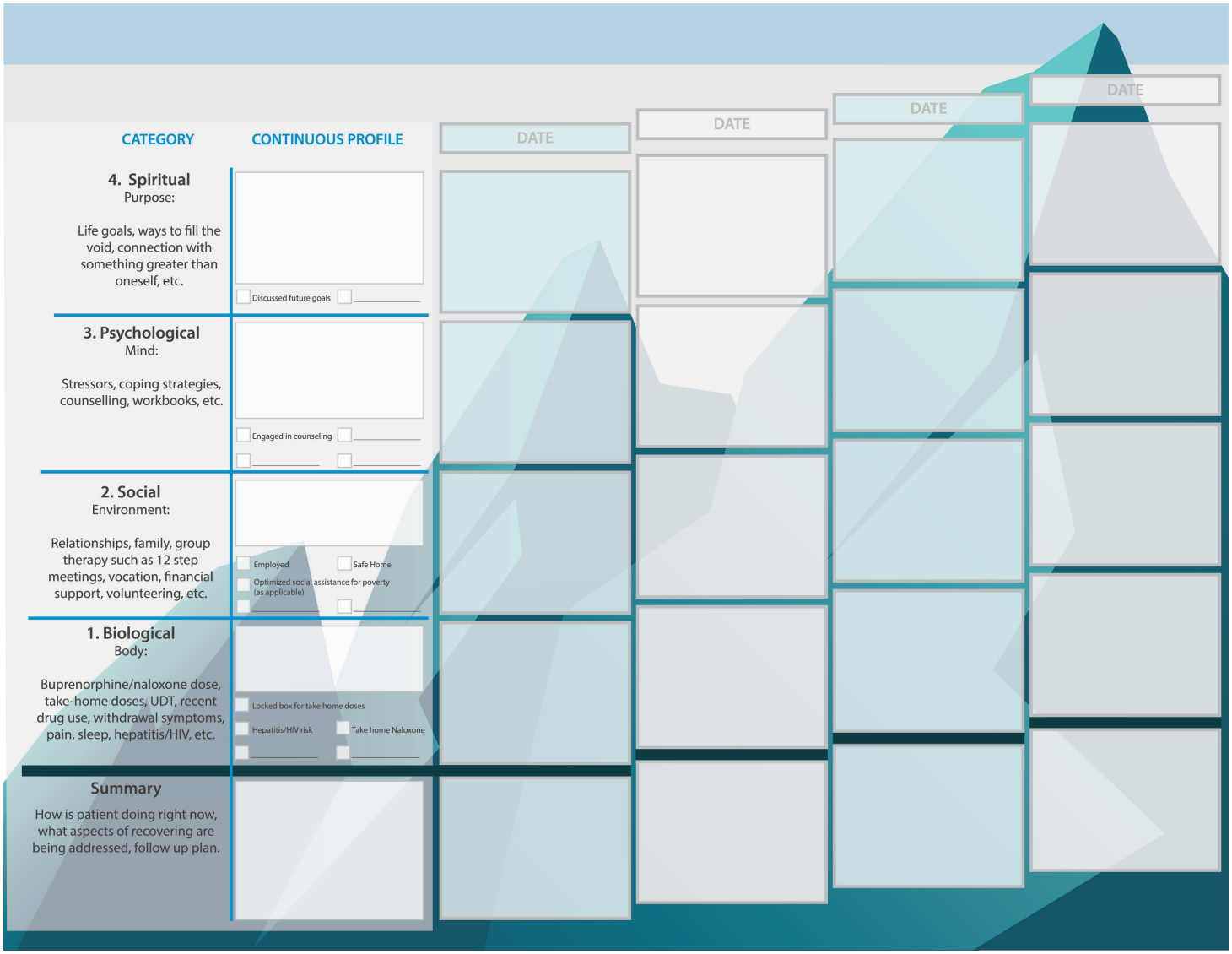
The diagnosis:
It is very helpful to remember here that "pain" and "addiction" are not mutually exclusive, black-and-white terms. It is best thought of as a spectrum. With patients on the addiction side, in an ideal world the patient is willing to acknowledge the problem. This is unfortunately often not the case, so instead we must rely on other means of assessing the patient. The main pattern with addiction is one of escalating use and increasing dysfunction, leading to further escalating use and further increasing dysfunction. Patients may try to hide this pattern - insisting that the opioids are helping them. By applying universal UDT to all patients with chronic pain prescribed opioids, we may pick up on subtle concerns, gradually tighten control/monitoring, and if addiction is finally established then we can intervene and support the patient accordingly.

Initial discussion:
Support, support, support! We are not here to punish anyone. We have very good biological treatments for opioid addiction and if we can maintain a therapeutic alliance then we can help reduce the patient's suffering. See Appendix F.

Overall approach:
While the majority of opioid use disorder in Canada is treated in high-volume specialty clinics, research suggests that better care is provided under the auspices of family physicians[1]. This is one reason that, if you have the time and energy to learn, it can be immensely beneficial to your patient - and rewarding to yourself - to offer Opioid Agonist Treatment (OAT) for opioid use disorder. While beyond the scope of this manual, we are working on doing for Opioid Use Disorder what we have done for UDT in chronic pain. We have simple innovations that address existing barriers and can help bring OAT into frontline family medicine. There are numerous educational resources available online - and new ones coming out regularly - but we think it's important to address the barriers to uptake at the level of frontline clinicians. This requires practical tools: simple, versatile and effective. Stay tuned for more about this initiative.

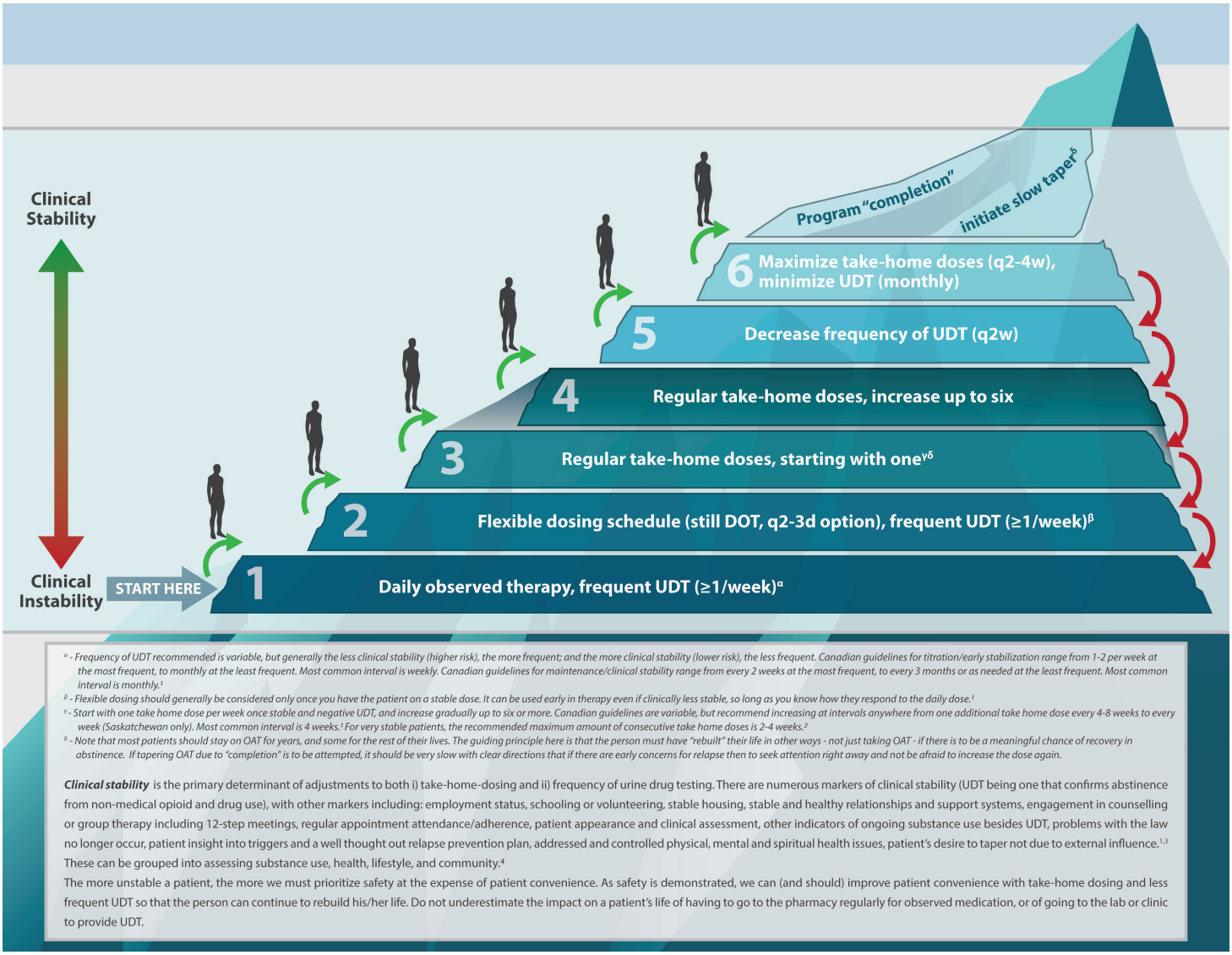
For the purposes of this manual, suffice it to say that every approach to addictions treatment involves reducing stress/pain/suffering, and/or improving coping/resilience. These strategies occur across the domains of biopsychosocial-spiritual (body, mind, environment and sense of purpose). Typically, earliest interventions address the biological aspects of recovery (eg. withdrawal) since it tends to be difficult to advance to deeper levels of recovery without first addressing these more superficial ones. The flowsheet infographic below demonstrates this approach as being analogous to climbing a mountain - with biological challenges being the first to ascend, followed by social, psychological and finally spiritual. This infographic is part of an addictions flowsheet that we have been using in clinical practice for over 5 years. It can be immensely valuable when a patient in the throes of addiction presents to clinic and his/her life seems so disastrous that you don't know where to begin. It also organizes notes easily. We are currently applying for grants to upgrade and improve the rest of our addictions flowsheet (not pictured here).

Buprenorphine/Naloxone Visit Flowsheet



The following infographic provides a common-sense visual for how we address take-home doses and UDT frequency when prescribing OAT. Essentially, clinical stability is the primary determinant, and UDT is simply one indicator of that clinical stability (others include stable relationships and housing, work, engagement in counselling, etc.). A more stable patient has more take-home doses and less UDT, and a less stable patient has less take-home doses and more UDT. In the unstable patient, less take-home-doses and more frequent UDT are in the interest of safety and come at the expense of patient convenience. Conversely, if someone demonstrates improving clinical stability (through UDT results and other markers), then in the interest of patient convenience and supporting one's recovery, decreasing the burdensome pharmacy visits and UDT is generally indicated.

Buprenorphine/naloxone Prescribing and Monitoring Ladder



α - Frequency of UDT recommended is variable, but generally the less clinical stability (higher risk), the more frequent; and the more clinical stability (lower risk), the less frequent. Canadian guidelines for titration/early stabilization range from 1-2 per week at the most frequent, to monthly at the least frequent. Most common interval is weekly. Canadian guidelines for maintenance/clinical stability range from every 2 weeks at the most frequent, to every 3 months or as needed at the least frequent. Most common interval is monthly.[1]

β - Flexible dosing should generally be considered only once you have the patient on a stable dose. It can be used early in therapy even if clinically less stable, so long as you know how they respond to the daily dose.[1]

γ - Start with one take home dose per week once stable and negative UDT, and increase gradually up to six or more. Canadian guidelines are variable, but recommend increasing at intervals anywhere from one additional take home dose every 4-8 weeks to every week (Saskatchewan only). Most common interval is 4 weeks.[1] For very stable patients, the recommended maximum amount of consecutive take home doses is 2-4 weeks.[2]

δ - Note that most patients should stay on OAT for years, and some for the rest of their lives. The guiding principle here is that the person must have "rebuilt" their life in other ways - not just taking OAT - if there is to be a meaningful chance of recovery in abstinence. If tapering OAT due to "completion" is to be attempted, it should be very slow with clear directions that if there are early concerns for relapse then to seek attention right away and not be afraid to increase the dose again.

Clinical stability is the primary determinant of adjustments to both i) take-home-dosing and ii) frequency of urine drug testing. There are numerous markers of clinical stability (UDT being one that confirms abstinence from non-medical opioid and drug use), with other markers including: employment status, schooling or volunteering, stable housing, stable and healthy relationships and support systems, engagement in counselling or group therapy including 12-step meetings, regular appointment attendance/adherence, patient appearance and clinical assessment, other indicators of ongoing substance use besides UDT, problems with the law no longer occur, patient insight into triggers and a well thought out relapse prevention plan, addressed and controlled physical, mental and spiritual health issues, patient's desire to taper not due to external influence.[1,3] These can be grouped into assessing substance use, health, lifestyle, and community.[4]

The more unstable a patient, the more we must prioritize safety at the expense of patient convenience. As safety is demonstrated, we can (and should) improve patient convenience with take-home dosing and less frequent UDT so that the person can continue to rebuild his/her life. Do not underestimate the impact on a patient's life of having to go to the pharmacy regularly for observed medication, or of going to the lab or clinic to provide UDT.

There are numerous resources out there that can help with the educational challenges around prescribing buprenorphine/naloxone agonist treatment. We have found the following particularly useful:

1. Bruneau J, Ahamad K, Goyer M-È, et al. Management of opioid use disorders: a national clinical practice guideline. CMAJ. 2018;190(9):E247-E257. doi:10.1503/cmaj.170958
2. Kahan M, Hardy K, Clarke S. Safe opioid prescribing and managing opioid use disorder: A pocket reference for primary care providers. December 2017. https://www.womenscollegehospital.ca/assets/pdf/MetaPhi/2017-12-19%20PCP%20safe%20opioid%20prescribing.pdf.
3. Kahan M, Srivastava A, Ordean A, Cirone S. Buprenorphine: New treatment of opioid addiction in primary care. Canadian Family Physician. 2011;57(3):281-289.

4. Ducharme S, Fraser R, Gill K. Update on the clinical use of buprenorphine: in opioid-related disorders. Can Fam Physician. 2012;58(1):37-41.

5. Handford C, Kahan M, Srivastava A, et al. Buprenorphine/Naloxone for Opioid Dependence: Clinical Practice Guidelines. 2011. http://cpsa.ca/wp-content/uploads/2015/07/buprenorphine_naloxone_CAMH2012.pdf.

6. MacMaster University Health Sciences. (2017) Opioids Clinical Primer. https://machealth.ca/programs/opioids_clinical_primer/

Note again that our next project (after HARMS) is to translate knowledge into practice with Opioid Use Disorder. We aim to increase uptake of buprenorphine/naloxone agonist treatment in primary care through formalizing and disseminating the innovative tools we have been using in our clinical practice for several years. While family physicians are being inundated with resources for more education around OUD and OAT, there is still a paucity of pragmatic clinical tools that help frontline physicians at the level of knowledge translation.

Cases

Case 1

A 40 year old male, who has been a patient of yours for many years, has requested early refills of his prescription several times in the last year. He has fibromyalgia, and you are currently prescribing oxycodone/acetaminophen 8 tabs/day. His wife came in for an appointment and tells you that her husband is buying medications from the street, his health is declining, he is depressed and generally unwell. When you discuss with him at his next appointment, he states he has to buy from the street because the oxycodone no longer controls his pain. What do you do? *This patient, by clinical Gestalt, appears to have OUD given that his use has been escalating as his function has been declining. Ideally you can get him on board to start treatment. See previous chapters for discussion points. In terms of actual treatment, this patient would be an excellent candidate for OAT with buprenorphine/naloxone. If he denies that he has OUD, then at your discretion you may consider prescribing buprenorphine/naloxone for pain (off-label - BID to QID) which has the added benefits over his existing oxycodone prescription of lower overdose potential, and tighter affinity for the opioid receptors (such that ongoing oxycodone use would not be rewarding to the patient). The induction of buprenorphine/naloxine is beyond the scope of this manual.*

Case 2

A 52 year old male has been a patient of yours for about 5 years. After a diagnosis of OUD 9 months ago, you started him on OAT right away with buprenorphine/naloxone. He was successfully titrated to a sublingual dose of 12 mg once daily Although he has complete relief of withdrawal symptoms and cravings, functions well, and is deemed clinically stable, you have noticed a sharp decline in his mood at the past two visits. After doing some probing, the patient opens up to you that even though he has improved his life, his opioid problem has caused a break down in the relationship with his kids. He states that "I physically feel good, but I feel as though I have no one outside of the clinic to talk to about my problems, and as a result, am feeling more and more anxious." How do you approach this situation?

This is an example demonstrating that OAT is only one aspect of treatment. Although he is doing well with the physical aspect of his recovery (withdrawal is controlled), there are other aspects of his life that may need to be addressed. There are other aspects of pain/suffering, in addition to the physical ones, that need to be addressed if patient is to maximize his chance of a successful long-term recovery. With the patient opening up, this is a great opportunity to advance in addressing the other aspects of recovery (such as seeing a counsellor). Beyond the scope of this manual, however considerations include the relationship with his kids, work, past-trauma, etc. A helpful forum to address these various issues may be 12-step meetings, addictions counselling, rehabilitation programs, etc.

Case 3

A 23 year old female has been treated for OUD with buprenorphine/naloxone at your clinic for about 6 weeks now. She is doing better and is maintained on a dose of 16 mg daily, however, her LC-MS UDT 2 weeks ago was positive for meth-amphetamine and clonazepam that is not prescribed. She discloses to you that she met up with an old friend two weeks ago and had taken the two drugs at a party. All other UDT's have come back negative. She comes in for a follow up appointment this week and asks about take home doses and why she has to provide a UDT every week. *This is a great opportunity to speak with the patient about take home doses and frequency of UDT. Remember that UDT is one marker of clinical stability. If this patient had an unexpected UDT, but was working again, in a new stable relationship, etc. then perhaps take-home dose(s) would be justified. Use your clinical discretion but remember that UDT is just one marker of clinical stability when considering how many take-home doses to give, and how often to conduct UDT. You can tell her that the frequency of UDT decreases as she demonstrates that she is doing well ("clinically stable").*

Chapter Pearls

- OUD is best treated in primary care. OAT with buprenorphine/naloxone is the first-line treatment for almost all patients with OUD.
- OAT is only one aspect of treatment for OUD. To have the best chance of long-term success, other aspects of recovery need to be addressed as wel.l
- Clinical stability is the main determinant of take-home doses and UDT frequency when prescribing OAT (very similar to the general idea in the HARMS Program for patients with CNCP, as demonstrated in the Risk Ladder). UDT is one marker of clinical stability.
- Harm reduction should be employed by providing naloxone kits to all patients prescribed OAT.

REFERENCES:

1. Perry D, Orrantia E, Garrison S. Treating opioid use disorder in primary care. Can Fam Physician Med Fam Can. 2019;65(2):117.

Appendix H: Tapering and Discontinuing Opioid Medication

Now that you have discussed tapering and discontinuing opioids with your patient, this section will provide some guidance on how to do the taper.

Reasons to consider tapering opioids:

- Patient request[1]
- Problematic opioid behaviour (see Appendix E. Monitoring for red flags beyond UDT)
  - Nonadherence to treatment plan[1]
- Clear evidence of opioid use disorder (see Appendix G Opioid use disorder)
- Adverse effects
  - Overdose or early warning signs for risk of overdose such as sleep apnea, hyperalgesia, and withdrawal mediated pain
  - Adverse effects are impairing functioning
  - Intolerable adverse effects
- Opioid doses exceed 90 MED[1]
- Lack of improvement in pain or function[1]
- Opioid in combination with benzodiazepines

Exercise CAUTION when tapering opioids in the following populations. Consider seeking expert opinion or additional consultation.[2]

- Pregnancy (premature labour, abortion with severe withdrawal)[3]
- Concerns taper will destabilize mental illness
- Concerns taper will destabilize or unmask substance use disorders (e.g. opioid use disorders)
- Medically unstable conditions such as severe hypertension or unstable CAD
- Diabetes mellitus - sick day management[3]
- Decreased cognitive function/cognitive impairment[2,3]

The Canadian guidelines[1] recommend discussing tapering in individuals (with CNCP) who are currently using ≥ 90 mg MME per day of opioid to lowest effective dose, and potentially discontinuing use.[1] Guidelines suggest doing so using an individualized approach to tapering.[2,4] Patients should be involved in the discussion that addresses benefits (better pain control and quality of life)[1] and harms of current opioid use, as well as the approach to the taper. In addition to the reason for the individual's taper, discussions should also include patient's goals and expectations. These conversations require empathy and mutual agreement for buy-in and adherence. If patients are not ready, the conversation can be revisited.[2]

It is of benefit to prepare the patient for the taper by optimizing non-opioid strategies for pain management, optimizing psychosocial support, and creating a schedule and plan for follow-up visits as well as managing withdrawal symptoms.[1]

General approach to tapering opioids as provided by the *Centre for Effective Practice Opioid Tapering Template* (2018) and the Canadian guidelines (2017):

- **Establish the opioid formulation to be used for tapering**
  - Switching from immediate release to controlled release opioids on a fixed dosing schedule may assist some patients with adherence[1]
- **Establish the dosing interval**
  - Scheduled doses help with pain control and withdrawal versus PRN doses
  - Maintain consistent dosing intervals (e.g. twice daily)
- **Establish the rate of taper based on patient health, preference and other circumstances**
- **Individualize tapering schedule**
  - For some this can be gradual and take months and for others years
    - Generally the longer the duration of previous opioid therapy, the more gradual the taper should be. For those with long-term use (> 5-10 years) or comorbid psychiatric conditions, a taper of >6 months may be required[3]

- A slow taper should be followed unless otherwise indicated (e.g. patient preference), especially if on >90mg ME/day[1]
  - A dose reduction of 5-10% of morphine equivalent dose every 2- 4 weeks with frequent follow up is reasonable in the community depending on how the patient tolerates the taper and their desire to taper[1,3]
  - The taper should be more gradual once the total daily dose reaches a lower dose range. For example reduce to 5% reductions every 4-8 weeks once at $^1/_3$ of previous used daily dosage[3]
- A **rapid taper** may be completed over 2–3 weeks[2]
  - CAUTION as reducing the dose immediately or rapidly over a few days or weeks may result in severe withdrawal symptoms. This is best completed under medical supervision at a withdrawal centre[1,2]

- **Follow up with the patient frequently (e.g. every 1–4 weeks)[2]**
- **Adjust the rate, intensity, and duration of the taper according to the patient's response (e.g. pain, function, withdrawal symptoms)**
  - Tapering may be paused and reassessed or potentially abandoned in patients who experience distressing pain, decreased function or withdrawal symptoms that persists for more than 1 month[1–3]
- **Optimize alternative (non-opioid) pain management strategies[2,3]**
- **Anticipate and treat withdrawal symptoms as needed[2,3]**
- **Taper to the lowest effective dose**

It may be useful to utilize a tapering plan form/document with patients to delineate a plan that is agreed upon by both the patient and practitioner. Ensuring the patient is engaged and part of the planning process is important for buy-in and adherence to the agreed upon plan. Although a tapering schedule is established initially it may need to be revised throughout the taper depending on how the patient responds to the taper. For an example of a tapering plan document see the CEP opioid tapering template: https://cep.health/media/uploaded/20180305-Opioid-Tapering-Tool-Fillable.pdf

SAFETY/CAUTION while tapering:
- Warn patients that tolerance can be reduced after as little as 1-2 weeks of a dosage taper.
- Give patients a naloxone kit or refer them to a pharmacy to obtain a kit so that in the event they relapse or resume their pretaper dose they won't overdose[3]

Opioid Withdrawal Symptoms

Early symptoms (hours to days)	**Late symptoms**	**Prolonged symptoms**
Anxiety/restlessness Sweating Rapid short respirations Rhinorrhea, tearing eyes Dilated reactive pupils Brief increase in pain	Rhinorrhea, tearing eyes Rapid breathing, yawning Tremor Diffuse muscle spasms Bone/joint aches Pilo-erection Nausea and vomiting Diarrhea Abdominal pain Dysphoria Fever, chills	Irritability Fatigue Malaise

Chart adapted from Rx Files

Other strategies to reduce, taper or discontinue opioids:

- Switch current opioid to another opioid and reduce MED by 25% to 50%[3]
- Switch to opioid agonist therapy such as buprenorphine-naloxone or methadone and then gradually taper[1]. A consult or referral may be required if the clinician is unfamiliar with the protocol for use of opioid agonist therapy[1,2]

The above approach to tapering has been summarized from the CEP Opioid Tapering Template. For the full document see https://cep.health/clinical-products/opioid-tapering-template/

For those patients (with CNCP) who have significant challenges with tapering (ie, re-emergence of new functional or psychological impairment or aberrant behaviours around opioid use), the Canadian guidelines recommend a formal multidisciplinary tapering program and consultation with local experts.[1] However, the availability of multidisciplinary team members may be limited to larger centres.

Cases

Case 1

64 year old male comes into the clinic to discuss his pain. He has been on opioids for 2 years - and is now on 60mg morphine SR BID for back pain. He has recently had some other health issues, with a new diagnosis of obstructive sleep apnea and diabetes. He is requesting a higher dose of opioids, but with further discussion you determine that he has never had much pain relief with his opioids. You discuss tapering his morphine and he is agreement. In collaboration you decide upon a gradual taper. You calculate his total daily morphine dose as 120mg/day. You determine that 5-10% of that dose is 6-12mg, however the available doses are only in 15mg increments. You agree to decrease him to 45mg in am and 60mg in pm to start, and follow-up with him in 2 weeks to reassess his pain and see how he is tolerating the taper.

Chapter Pearls

- Tapering should be individualized and plans made in collaboration with the patient.
- A slow taper should be followed unless otherwise indicated (e.g. patient preference).[1,2]
- A dose reduction of 5-10% of morphine equivalent dose every 2- 4 weeks with frequent follow up is reasonable in the community.
- Tapering may be paused and reassessed or potentially abandoned in patients who experience distressing pain, decreased function or withdrawal symptoms that persists for more than 1 month.

REFERENCES:

1. Busse J. The 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain. 2017.
2. Centre for Effective Practice. Opioid Tapering Template. February 2018. https://cep.health/media/uploaded/20180305-Opioid-Tapering-Tool-Fillable.pdf. Accessed August 14, 2019.
3. Rx Files. Tapering Opioids. How to Explore and Pursue the Option for Patients Who Stand to Benefit. Chronic Pain/Opioids Part 2. Spring 2018. https://www.rxfiles.ca/rxfiles/uploads/documents/Opioid-Tapering-Newsletter-Compilation.pdf. Accessed August 14, 2019.
4. Centers for Disease Control and Prevention (CDC). Pocket Guide: Tapering Opioids for Chronic Pain. https://www.cdc.gov/drugoverdose/pdf/clinical_pocket_guide_tapering-a.pdf.

Appendix I: Treatment Agreements and Patient Consent

This section provides some more detailed information on treatment agreements and consent for UDT...

Treatment Agreements (consent to HARMS Program)

Current Canadian guidelines (2017) note that evidence on treatment agreements is of low-quality and shows limited benefits, with equivocal effects on opioid misuse[1]. Despite the lack of high quality evidence, treatment agreements can be utilized as a method of gaining informed consent on opioid use and clarifying expectations for both the patient and physician. Written agreements can delineate the terms and goals of an opioid trial, points of termination, and alternative treatments in the event of a failed trial[1]. The use of treatment agreements is optional and can be modified to reflect physician prescribing.

HARMS Program Treatment Agreement

You are being asked to complete a treatment agreement because you are prescribed medication(s) that may pose a safety risk. By signing a treatment agreement, it promotes communication between you and your doctor, helps avoid misunderstandings and improves your safety with the prescribed medication as much as possible.

I understand that I am being prescribed opioid medication from _____ (doctor/nurse practitioner/clinical group) to treat my pain condition. I agree to the following:

1. I understand that the prescriber and I will work together to find the most appropriate treatment for my chronic pain. Chronic opioid therapy is only ONE part of my overall pain management plan (acupuncture, massage, chiropractic, yoga, mindfulness, traditional healing, staying active, etc).
2. I understand that common side effects of opioid therapy include: constipation, nausea, sweating, and itchiness of the skin. Drowsiness may occur when starting an opiate medication or when increasing the dosage. I agree to refrain from driving a motor vehicle or operating dangerous machinery until such drowsiness disappears.
3. I will not seek opioid medications from another physician. Only the "prescriber" listed above will prescribe opioids for me.
4. I will not take opioid medications in larger amounts or more frequently than is prescribed by the prescriber.
5. I will not give or sell my medication to anyone else, including family members; nor will I accept any opioid medication from anyone else.
6. I will not use over-the-counter opioid medications such as 222's and Tylenol® No. 1.
7. I understand that if my prescription runs out early for any reason (for example, if I lose the medication, or take more than prescribed), the "prescriber" will not prescribe extra medications for me; I will have to wait until the next prescription is due.
8. I will fill my prescriptions at one pharmacy of my choice; pharmacy name: _____
9. I will store my medication in a secured location.
10. I agree to provide periodic urine samples for the purposes of drug testing. This is a universal safety precaution used at this clinic.
11. I agree to a planned process to reduce and/or discontinue the opioid if goals/benefits are not realized or harms outweigh benefits.

I understand that if I break these conditions, the prescriber may choose to cease writing opioid prescriptions for me.

Patient Name:_____

Date:_____/_____/_____

Adapted and modified from Kahan 20061 and RxFiles[2]

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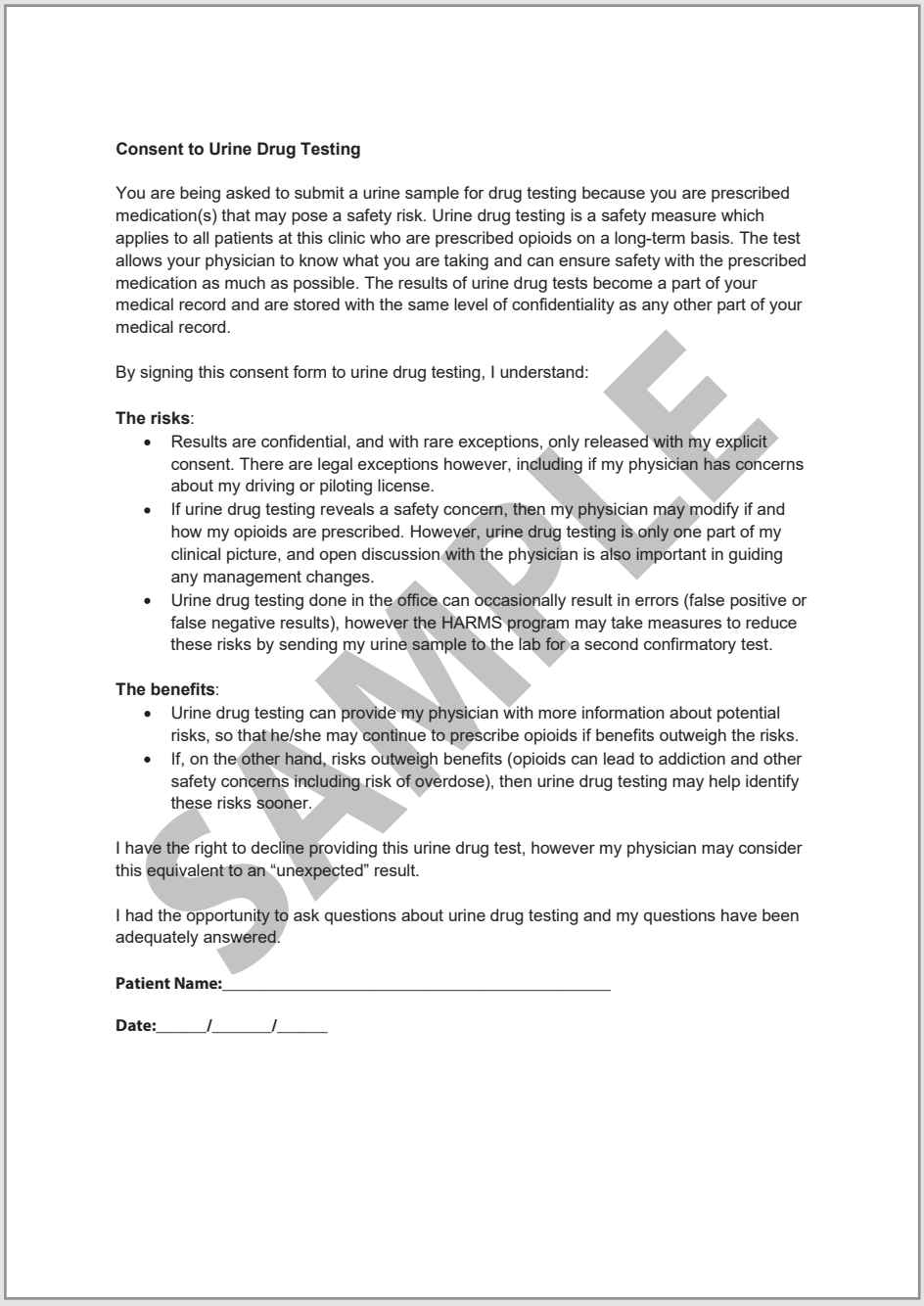
Consent to Urine Drug Testing

The primary goal of urine drug testing (UDT) is to improve the safety and efficacy of opioid therapy by monitoring adherence. UDT provides clinicians with an objective measure to support decision making during opioid prescribing.[3] Expert opinion strongly recommends urine drug testing be utilized as a universal precaution.[3]

As part of the HARMS program, patients are randomized to complete urine drug testing according to their risk level. Each time a patient is requested to complete UDT, they should consent. Below is an example of a consent outlining the risks and benefits of urine drug testing.



Consent to Urine Drug Testing

You are being asked to submit a urine sample for drug testing because you are prescribed medication(s) that may pose a safety risk. Urine drug testing is a safety measure which applies to all patients at this clinic who are prescribed opioids on a long-term basis. The test allows your physician to know what you are taking and can ensure safety with the prescribed medication as much as possible. The results of urine drug tests become a part of your medical record and are stored with the same level of confidentiality as any other part of your medical record.

By signing this consent form to urine drug testing, I understand:

The risks:

- Results are confidential, and with rare exceptions, only released with my explicit consent. There are legal exceptions however, including if my physician has concerns about my driving or piloting license.
- If urine drug testing reveals a safety concern, then my physician may modify if and how my opioids are prescribed. However, urine drug testing is only one part of my clinical picture, and open discussion with the physician is also important in guiding any management changes.
- Urine drug testing done in the office can occasionally result in errors (false positive or false negative results), however the HARMS program may take measures to reduce these risks by sending my urine sample to the lab for a second confirmatory test.

The benefits:

- Urine drug testing can provide my physician with more information about potential risks, so that he/she may continue to prescribe opioids if benefits outweigh the risks.
- If, on the other hand, risks outweigh benefits (opioids can lead to addiction and other safety concerns including risk of overdose), then urine drug testing may help identify these risks sooner.

I have the right to decline providing this urine drug test, however my physician may consider this equivalent to an “unexpected” result.

I had the opportunity to ask questions about urine drug testing and my questions have been adequately answered.

Patient Name:_____

Date:_____/_____/_____

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Cases

Case 1

43 year old male coming in for a refill of his oxycodone/acetaminophen 6 tabs/day. He is new to your clinic. You do your intake history and physical and inform him of the HARMS Program. He signs the treatment agreement but is skeptical to sign the urine drug testing consent. He is a truck driver and voices concern over the possibility of his test results being shared with his employer. You reinforce laws surrounding confidentiality and that the results would not be shared with his employer. You inform him that you would discuss any concerns with his safety to drive with him prior to any action, and if any action was required, it would involve reporting to the ministry.

Chapter Pearls

- Use of treatment agreements is optional. Low quality evidence shows limited benefits, with equivocal effects on opioid misuse.

REFERENCES:

1. Busse J. The 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain. Cancer Pain. 2017:105.
2. Rx Files. Informed Consent/ Agreement for the Use of Opioid Medication in Chronic Pain. https://www.rxfiles.ca/rxfiles/uploads/documents/Opiod-Informed-Consent-And-Agreement.pdf. Accessed August 15, 2019.
3. Argoff CE, Alford DP, Fudin J, et al. Rational Urine Drug Monitoring in Patients Receiving Opioids for Chronic Pain: Consensus Recommendations. Pain Med Malden Mass. 2018;19(1):97-117. doi:10.1093/pm/pnx285

BPI = Brief Pain Inventory

The BPI is a validated tool that measures a patient's pain and functional impairment. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory.Ann Acad Med Singapore 23(2): 129-138, 1994).
Find out more here:

https://www.mdanderson.org/research/departments-labs-institutes/departments-divisions/symptom-research/symptom-assessment-tools/brief-pain-inventory.html and find a copy here:

http://nationalpaincentre.mcmaster.ca/documents/brief_pain_inventory.pdf

CNCP = Chronic non-cancer pain (generally also means "non-palliative" pain)

HARMS was built for UDT in this population. Patients with cancer and/or palliative pain are typically excluded. Chronic pain is typically defined as >90 days or past the time of normal healing.

COMM = Current Opioid Misuse Measure

A self-report screener that detects problematic opioid-related behaviours in patients with pain who are receiving opioid therapy. Stacey A McCaffrey, Ryan A Black, Albert J Villapiano, Robert N Jamison, Stephen F Butler, Development of a Brief Version of the Current Opioid Misuse Measure (COMM): The COMM-9, Pain Medicine, Volume 20, Issue 1, January 2019, Pages 113–118, https://doi.org/10.1093/pm/pnx311.
Learn more about it here:

https://ibhsolutions.com/blog/questions-comm-9-answered/

DIRE = Diagnosis, Intractability, Risk, and Efficacy Score

The DIRE is a clinician-rated instrument designed for use by primary care physicians to predict the efficacy of analgesia and adherence with long-term opioid therapy. The DIRE score can range from 7 to 21, with a score of 13 or below suggesting that a patient is not a suitable candidate for long-term opioid therapy. Belgrade MJ, Schamber CD, Lindgren BR. The DIRE score: predicting outcomes of opioid prescribing for chronic pain. J Pain. 2006;7(9):671-681.
You can find the DIRE tool here:

http://www.emergingsolutionsinpain.com/content/tools/esp_9_instruments/pdf/DIRE_Score.pdf

GC-MS/MS = Gas chromatography tandem mass spectrometry

This is an older variation of LC-MS/MS which many laboratories still use for their drug confirmatory testing today. Laboratories are switching to LC-MS/MS when possible due to the newer test's ability to analyze more compounds at once and the process is much less labour intensive.

HARMS = High-yield Approach to Risk Mitigation and Safety.

HARMS is a clinic-wide system built to support routine urine drug testing in clinical medicine. There are specific innovations within the HARMS Program that aim to address previous barriers to UDT in clinical medicine (START-IT Tool, Risk Ladder, general program structure that delegates to non-medical staff, and others). HARMS has won awards at the provincial and national levels for innovation and scalability.

IA = Immunoassay

Also sometimes called "Point-of-care", or "presumptive testing", this is the method of UDT that is applied in the office (although lab can also do it). Urine is collected and "dipped" using the kit. Results are available within minutes, and the test is relatively inexpensive (we pay $4.50 for each standard 5-panel test). Unfortunately it is generally less sensitive and less specific than LC-MS. There are panels available commercially for numerous drugs with varying sensitivities and specificities.

LC-MS/MS = Liquid chromatography tandem mass spectrometry

Also sometimes called "confirmatory testing", this is done by the lab. While it takes 1-2 weeks for results, it has a very important role because it's specificity is theoretically 100% (assuming no human error in documentation or sample mix-up). It also checks for >100 drugs (exact drugs will vary depending on the lab).

OAT = Opioid agonist treatment.

There are numerous other terms (Opioid substitution therapy, opioid maintenance therapy, etc.) that refer to typically using either methadone or buprenorphine/naloxone prescribed in a controlled setting to treat opioid use disorder by addressing opioid withdrawal and cravings. 2018 Canadian guidelines (CRISM) specifically recommend buprenorphine/naloxone as the first-line treatment for opioid use disorder.

ORT = Opioid Risk Tool

The ORT is a validated tool that uses patient self-report to assess risk of developing opioid use disorder when prescribed opioids for chronic non-cancer pain. Questionnaire developed by Lynn R. Webster, MD to assess risk of opioid addiction. Webster LR, Webster R. Predicting aberrant behaviors in Opioid-treated patients: preliminary validation of the Opioid risk tool. Pain Med. 2005; 6 (6) : 432).
Find it here:

https://www.drugabuse.gov/sites/default/files/files/OpioidRiskTool.pdf

OUD = Opioid use disorder.

Colloquially known as opioid addiction, and in previous versions of the Diagnostics and Statistics Manual (DSM) called Opioid abuse or opioid dependence. There are 11 specific criteria and depending on how many criteria are met it may be mild, moderate or severe.

SOAPP-R/ SOAPP-8 = Screener for Opioid Assessment for Patients with Pain - Revised

SOAPP-R is used to risk stratify patients prescribed opioids for CNCP for future problematic behaviours. (Ryan A Black, Stacey A McCaffrey, Albert J Villapiano, Robert N Jamison, Stephen F Butler, Development and Validation of an Eight-Item Brief Form of the SOAPP-R (SOAPP-8), Pain Medicine, Volume 19, Issue 10, October 2018, Pages 1982–1987, https://doi.org/10.1093/pm/pnx194).
Learn more about it here

https://ibhsolutions.com/blog/questions-soapp-8/

START-IT = Self-report, Testing and Automated Reading Tool for Immunoassay Tests.

START-IT is a national-award winning IT tool that is typically applied using a tablet PC by non-medical staff at the clinic. It aims to greatly simplify the entire UDT process at the clinic through the collection of all the required information for UDT result interpretation: prescribed medication and last dose, self-reported non-prescribed drugs and last use, and immunoassay test results themselves. Results are then interpreted within the limitations of the test (false positives, false negatives) and clinically-relevant explanations are given about what the result means. If using the OCEAN platform, then report syncs with most Ontario EMRs with the click of a button. We have never had any monetary gain from START-IT, always offering it for free (however if using the OCEAN platform - completely unaffiliated - then they have a monthly subscription fee).

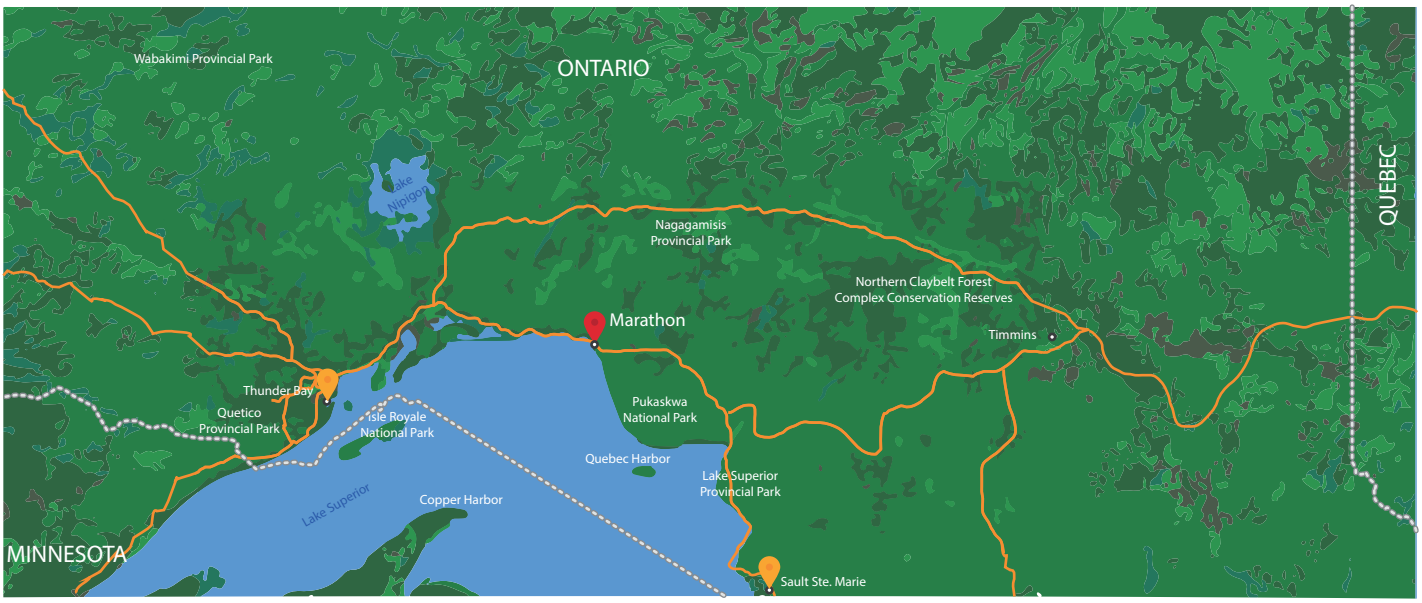
UDT

Urine drug testing.

UrIntepret

A smartphone application we designed to give rapid and comprehensive UDT interpretation, including IA and LC-MS. The application also includes the START-IT tool and high-yield interactive Clinical Cases.

About The Authors



Marathon is a town with a catchment area of 3913 people located between Thunder Bay and Sault Ste. Marie in Northern Ontario. The Marathon Family Health Team is a group of anywhere from 6-9 family physicians, as well as numerous allied health professionals (RNs, RPNs, PA, NP, SW, etc.) that provide comprehensive care to Marathon and the surrounding communities of Pic Mobert First Nations and Biigtigong First Nations. There are no Royal College specialists of any kind for 300km (Thunder Bay is our closest referral centre).

Although HARMS and START-IT were founded at the MFHT, the MFHT is an independent entity and is not responsible for any of the information published here.

About the authors:

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After completing his MD at the University of Toronto in 2011, Dr. Patchett-Marble completed his rural family medicine residency based out of the Northern Ontario School of Medicine (Thunder Bay). Since 2013, he has worked as a rural generalist in Marathon ON. His medical practice includes family medicine, emergency medicine, hospitalist, and addictions medicine. He is currently an assistant professor at NOSM. His interest in clinical innovation led to founding the HARMS Program and START-IT Tool.

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Adrian Grebowicz is currently a medical student at the Northern Ontario School of Medicine (Class of 2022). He was involved with the Opioid Use Disorder chapter and the associated infographics.

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NOAMA

NORTHERN ONTARIO ACADEMIC MEDICINE ASSOCIATION

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