Minutes: Fourth Meeting of the Pragmatic Trials Interest Group: 09/07/2019

Attended: Nick Lintzeris, Anthony Shakeshaft, Kristie Mammen, Krista Siefried, Libby Topp, Sarah Farnbach, Llew Mills, Emma Black, Nadine Ezard

Apologies: Raimondo Bruno, Shikha Agrawal, Rachel Deacon

Chair: Llew Mills

Topic 1: Pragmatic trials portion of the MAData project

Systems Test of Data Gathering Infrastructure: Faux-Randomised Trial

NE indicated her hunch that people using a lot of opioids at intake usually prefer to start, and are more stable, on methadone than Buprenorphine.

NE and RD emphasised the need to be able to extract 'type of OTP treatment' data from eMR, especially what drug clients are being prescribed (Bup vs Methadone). NE said we might consider the process of streamlining the extraction of Type of Treatment data to be one of the outcomes of MAData.

NE emphasised the importance of clearly defining who qualified as MA-using in the OTP treatment population. RB suggested in a previous meeting weekly or more would make a good criteria. LM has developed a data-driven approach using a mixture model that could answer this question. Will explore this and get back to the group.

NL indicated that Type of Treatment information should be extractable from CHOC/iDose but only for clients who are collecting their dose from SESLHD sites. LM to follow up how to extract this info from iDose.

The following are still the questions that we will ask for the MAData systems test. LM to devise operationalised versions of these after consultation with Jennifer Holmes. For this systems test the **predictor** will be methadone vs bupe (this is only a way of 'faux-randomising' clients and not necessarily of clinical interest, but 'is' the sort of thing that could conceivably be randomised in a clinical trial. The **outcomes** will potentially be:

(i) How are the profiles (age, gender, employment, frequency of use of primary and secondary drugs of concern, contact with legal system, number of dependents, injecting vs non-injecting, housing situation, psychological health, physical health, and quality of life) of MA-using OTP clients and non-MA-using OTP clients different? This would be measured at a single-time point (i.e. cross-sectional). From existing COQI Cohort Data

(ii) How do treatment outcomes (e.g. frequency of illicit drug use) differ among MA-using OTP clients and non-MA-using OTP clients? This would be a longitudinal analysis, restricted to those clients who had multiple ATOPs collected in a single encounter. *Existing COQI Cohort Data*

(iii) How different is the *quality* of data between the two groups? i.e. is there less data collected for OTP clients who use MA (reflecting more chaotic life)? *Restrict this to COQI Cohort Data?*

(iv) Do MA-using OTP clients take up more service resources (e.g. more clinical consultations, referrals to social workers, psychologists, admin time) than non-MA users? LM to enquire with Kristie and Jennifer Holmes about how to use QI data
(v) Do MA-using OTP clients benefit more from assertive follow-up than standard follow-up?
(vi) Are MA-using OTP clients more chaotic than non-MA-using OTP clients (e.g. more missed doses (measurable through number of DAARFs, COWS, and through iDose) more incidents at clinic (this is not answerable with IIMS because it is not linked to patient name)

RB has noted that using weekly or more should be the criteria for inclusion in the MA-Using-OTP clients group.

The analyses above would require extraction, cleaning, and analysis of eMR data. Through the COQI cohort study we currently have access to all SESLHD AOD data from 2016-present.

Questions from Agenda:

1. Do we want to use data from SESLHD only or also from Vinnie's, Central Coast, ISLHD, North Sydney, HNE? *We will start with SESLHD*
2. When do we want to start the analysis process? *ASAP*
3. Who will do it? *LM to take care of most of the data analysis*

Topic 2: Setting Up Capacity for Future Pragmatic trials

The discussion centred mainly on how to get the process of consulting clinicians about potential research questions. NL suggested that setting up a process for consulting clinicians about what part of their jobs or treatment of clients could be improved was the most important part of the project.

NL suggested that clinicians may not be trained or inclined to formulate research questions in a way that allowed them to be operationalised, but that these same clinicians had extensive processes in place already for identifying problems and improving treatment. So they *will* know what areas need improving. As researchers it is our job to take their observations and (i) translate them into cogent research questions, (ii) do the necessary literature search to identify whether these are questions that already have answers. Once researchers have performed these tasks they should have a list of tractable and novel *research* questions that can be presented to a larger group of clinicians across the participating LHDs for approval.

The Langton centre is having a research planning day where we will attempt to crystallise the process. In the meantime LM and LT will attempt to find ways to sit in on clinician discussions of day to day clinical care (e.g. handover meetings) to listen to clinicians discuss their business and start to make notes on when discussions become more general e.g. about recurring problems, frustrations, or issues.

The group re-iterated the need to frame all of this in terms of finding ways to improve treatment instead of finding interesting research questions, as the latter makes D & A treatment improvement sound like an amusing parlour game for academics rather than a way to improve outcomes for clients.

The group also re-iterated the need to have consumers take part in the process of research question formulation

Actions

1. LM and RD to see about extracting type of Treatment from CHOC, and to answer the question 'What proportion of clients have medication information completed in CHOC?'
2. LM to commence data analysis for Prag Trials section of MAData
3. LM to enquire from Tess Finch and Therese Chan how to extract iDose data: Consult RD, who can already extract *some* OST type information from CHOC
    - LM met informally with Joe Leung (Langton Pharmacist) and he answered the following questions:
        i. *Does iDose have MRNs attached?* MRN not attached to client record but is entered manually by Nurse when patient is registered
        ii. *Who is data custodian for iDose?* Joe did not know but said Matthew Peers is IT director for iDose. Ask Tess about this.
        iii. *Where is medication history for Amb Care Clients entered?* At the moment it is
            - entered manually in Clinical Notes in eMR
            - iPharmacy (see Therese Chan about this)
            - *Should* be entered in 'Orders' filed in eMR, but isn't. Therese Chan currently spearheading Best Possible Medication History (BPMH) a push to enter medication details in drop-down boxes for easy extraction
        iv. *Where is iDose data stored?* Ask Tess about this
4. LM to determine a good cutoff for 'MA-using'. Will need access to the SESLHD COQI Cohort ATOP + NMDS data.
5. LM to operationalise these questions by mapping them onto existing data items from the data list sent to the group.
6. LM to enquire with KM and Jennifer Holmes about how to access QI data (e.g. activity data)
    - Available from ORBIT (SESLHD dashboard), available by application to SESLHD performance unit.
7. At next meeting KM to show dynamic data summary software developed at Langton for displaying eMR data.

Example Pragmatic Trial Research Questions

The group has already proposed some research questions (below). The purpose of recording these questions is to start a sort of 'ideas bank', which need not be restricted to a pragmatic trial. I hope to add to this ideas bank with research questions driven by clinicians once the clinician consultation process begins in earnest.

There seems to be a strand of Bupe-Depot related questions emerging. NL suggested we may be a year off testing any of these properly since the Depot is only being used by a handful of clients, but it may be beneficial to start cataloguing research ideas around this question.

Potential Research Questions:

- NL discussed the potential of Bupe Depot vs Daily Dosing as an area of study. Could even be applied to MA-using OTP clients: 'Do MA-using OTP clients benefit more from Bivudal than daily dosing (due to no missed doses).

- If clients undergoing a dose taper volunteer to have the exact timing and magnitude of their dose reductions concealed, do they experience less severe withdrawal symptoms than clients who are aware of the exact timing and magnitude of dose reductions?
- If clients are reminded by text message prior to appointments does it make it more likely that they will attend?
- Do clients receiving a single monthly injection of Bupe Depot each month report more severe withdrawal symptoms during that month than: (i) clients who receive monthly injection plus three weekly placebo injections each month, (ii) clients who receive four weekly injections. (Note: These questions highlighted only because AS refers to them below)
- what treatment approaches work best for people with poor cognition?
    - do those assessed with poorer cognition have higher levels of BZD use at tx entry? Does their BZD use drop off over the course of tx? (my non-clinician brain would hope that this is seen as a treatment target)
    - do people assessed with poorer cognition drop out of treatment services earlier than those with lower problems? (after controlling for PDOC and extent of use)
    - I would expect that this would be the case in the cannabis clinics
    - Are there different correlates of 'good outcome' for people with poorer cognition than for those without? (however we define 'good outcome' – but this has to be more than just days of illicit use – as per discussion in yesterday's meeting) – is it just treatment 'dose' or are there other factors? This may trigger more detailed RCT to test out any correlates
- do people with poorer cognition do better (based on days illicit opioid use; retention; 'success' however defined inc QoL) with daily ORT dosing than monthly depot? (probably just sticking to daily bup vs monthly bup)
- Clinician ratings of client complexity. This variable (depending on its validity and the clinical context in which it is asked) might be a compromise between deciding ourselves on research questions, and genuinely consulting with clinicians. So, would it be of interest to clinicians to know empirically what underlies their scores on this scale? This question might be phrased as, what are the differences between clients who score higher and lower on this rating scale, or the most significant contributors/predictors of the score? Could be client characteristics e.g., PDOCs, polydrug use (e.g., concurrent use of MA or BZDs), recently released from prison, comorbid mental health, housing, violence; or could be about resources required to manage them – either more resources because they are demanding and burdensome, or less resources because they only present intermittently).

Notes from Absent Friends

Notes from Sara Farnbach (absent):

- I like your point under 'topic 2' setting up the Clinical Leadership Groups. The way the teams here would identify questions would be from the 'pressing clinical need', which includes a thorough, iterative process of talking with clinicians (as many as you can get, from as many perspectives as you can), managers, patients, data teams, administrators, over time to see what the pressing questions / unknowns are. At the same time thinking about feasibility of data (does data answer the question we want, accurately? Does data systems need to be amended? Can it be? Would the proposed intervention/treatment work in practice?). This is what you're proposing, so I think that makes sense. For this reason I don't think I'm qualified as non-clinical and not working in the setting to come up with a specific question (sorry, not very helpful!).

- The MAData project (love the name!) sounds exciting. A system test sounds logical too. There may be some overlap with the Seed funding grant was just awarded to Craig Rodgers, Anthony, Daisy, Krista, Nadine and others. I don't know if we had this at the last meeting, so not sure if it was already discussed: this is a grant to do an audit of the OAT clients at Vinnies. This is really early days, but the idea is, once we get the audit underway, to see if a pragmatic trial could come out of this in the future. It sounds like this may be similar to MAData so I'm wondering if these are already linked, if not, if there is potential to do so? Apologies if I am re-hashing old conversations.

- Finally, here is an opioid use disorder ED-based pragmatic trial that may be of interest if you haven't seen it already. https://rethinkingclinicaltrials.org/demonstration-projects/ug3-project-pragmatic-trial-of-user-centered-clinical-decision-support-to-implement-emergency-department-initiated-buprenorphine-for-opioid-use-disorder-embed/

Notes from Anthony Shakeshaft (absent):

AS – further development of the depot idea

Background – these are just a series of thoughts to try to set the framework. More for discussion to help us continue to work through what we think pragmatic trials / learning systems actually are and how they differ from standard clinical trials.

- NL discussed the potential of Bupe Depot vs Daily Dosing as an area of study. Could even be applied to MA-using OTP clients: 'Do MA-using OTP clients benefit more from Bivudal than daily dosing (due to no missed doses).

- Agree this has good potential. Last time we met I wrote down (on my best friend the white-board) "given bupe depot is on the way we can utilise its uptake in practice to try to improve the precision of how we think bupe should be used in practice."

- My thinking has already been influenced by the conversations over here in Boston, and I am shamelessly riding on the back of the work that Sara has done with the people here. To me the risk is that we could answer a (very clinically useful) depot vs dosing question using some version of a standard clinical trial. But because we have this bupe roll-out introductory period then we have the potential opportunity to try to think about creating an embedded learning system (or at least an environment for pragmatic trials. But either way, I think we want to steer away from standard clinical trials…)

- Sara has done a bit of thinking about how to define the difference between a clinical trial type process and a learning health care system process, which will be really helpful for us to discuss at our net meeting when she's back. But, in practice, it may mean that it might be possible to combine the highlighted yellow questions in Llew's list into one trial that is about trying to learn as we go, that is, create a data-based learning system rather than just test one 'issue' vs another 'issue' (which is the standard sort of clinical trial protocol). I'm acutely aware that a little knowledge is a dangerous thing so I'm definitely not sure about any of this – hoping we can challenge it and work through the logic together.

- So here is a list of some of the potential 'real-world' or pragmatic issues around depot (taken from Llew's list):

- What are the possible bupe treatments that a clinician could provide (so we're not talking about anything here other than ways of providing bup - right?)
  a) Depot or non-depot (non-depot has to be daily dosing)
  b) Depot could be single monthly injection
  c) Depot could be four weekly injections
  d) Clients may be aware or unaware of the tapering of their doses

  And in this context there is the additional layer of patient choice. This might need some discussion – how much of an agreed treatment regime is truly patient choice vs clinical advice? Does it matter? (this is not a D&A-specific treatment issue…)

- How might a learning system treat these options? These clinical issues can be transposed into a series of 'rules' – and one of the rules is the best treatment for the majority of clients (ideally we'd get to the point where we can determine the best rule for each individual based on their characteristics – which is something we might be able to learn from the roll out of depot bupe, or at least get some testable hypotheses – but I suspect that approach will be very data heavy – something we could work towards over the next 5 years…). So let me test this logic:
  - There are three possible treatments:
    - depot single monthly injections;
    - depot four-weekly injections; and
    - non-depot daily dosing.

  - These three treatments could be used independently of each other, or in various combinations (perhaps a different combination for different patients) that relate to different phases or 'outcomes' of treatment, namely:
    i) outcome 1 = safe and comfortable withdrawal;
    ii) outcome 2 = achieve short-term (one month?) stability; and
    iii) outcome 3 = effective maintenance.
      - Maybe outcomes (i) and (ii) amount to the same thing?
      - There would need to be clear definitions for these as clinically meaningful outcomes. For example: i) clients experiencing minimal withdrawal symptoms; ii) clients achieving 'stability' (perhaps defined as something like attending at least 75% of dosing appointments, and/or 3 or 4 consecutive stable doses, and or stable ATOP scores); and iii) clients maintaining their engagement with treatment (again perhaps defined as getting at least two-thirds of their scheduled doses and/or stable ATOP scores). This seems a bit like the old school idea of three phases of treatment: withdrawal management, achieving stability, and maintenance. Seem ok? I do like that it gives us 3 'hard/clinically meaningful' outcome points to help with clarity about which clinical strategies are aiming to achieve which outcomes.
      - I think we are doing clinical services a disservice if we only define their 'success' in terms of the ongoing maintenance – there are likely to be measureable benefits for clients from successful detox and/or getting stable for a while, even if they relapse (although I think we need to be careful about the number of repeated detox episodes clients have…?). And, (this is perhaps my bias) I think it's better for evaluation to have a measureable, clearly defined outcome (purely for evaluation, it seems

dissatisfactory to say that the only 'good' outcome is continual treatment….)

- Sitting around these three possible treatments / combinations of treatments are some factors of unknown importance: i) do outcomes vary if treatment is a consequence of patient or clinician choice?; and ii) various demographics/client characteristics (e.g. do meth users do better on depot than non-depot). In passing, we could test these experimentally using point-of-care randomisation – patients can choose what they want and if they don't care they get randomised.

- Given NL's clear view (I think) that depot will be better for meth clients (either just in terms of outcomes 1 and 2, or all 3 outcomes), then it might be worth building that into our clinical 'rules'. We could use the initial roll-out of depot to predict if this is true…

- So in our context, these three treatment options could be transposed into nine rules (and these might need to be applied separately to each agreed outcome). And the task of the pragmatic trial/learning system is to systematically determine which of these rules is the best (for now, the best = the best outcome on average across all clients but in time we might be able to define a best 'rule' for each individual client – now that's individualised medicine!).

- Some of the possible nine rules are clearly unlikely to turn out to be the 'best rule' (for example, it would be surprising if rules 8 and 9 were the best) but the important thing is that they are the clinical options, and our learning system has to identify which of these rules is, on average, the best clinical outcome for all clients:
    1. Everybody gets a depot single monthly injection
    2. Everybody gets depot four-weekly injections
    3. Everybody gets non-depot daily dosing
    4. Meth clients get a depot single monthly injection and non-meth clients get depot four-weekly injections
    5. Meth clients get a depot single monthly injection and non-meth clients get non-depot daily dosing
    6. Meth clients get depot four-weekly injections and non-meth clients get depot single monthly injection
    7. Meth clients get depot four-weekly injections and non-meth clients get non-depot daily dosing
    8. Meth clients get non-depot daily dosing and non-meth clients get a depot single monthly injection
    9. Meth clients get non-depot daily dosing and non-meth clients get depot four-weekly injections

- In this context, the 'bad' outcomes are when clients gets the wrong rule. The dynamism in the learning system can be identifying when it is the wrong rule for each client and shifting him/her over to a different rule. I think this gets us into

the territory of adaptive trial design. Of course, while the system is 'learning' that can lead to a good outcome (a client moves from the wrong rule to the right rule) or a double bad outcome (a client moves from one wrong rule to another wrong rule). I don't think there's any way around that – the best we could do is harm minimisation! Monitor it as closely as we can and change the rules as soon as it looks like it is ineffective for that client. I hasten to add that I'm not sure we'll be at this dynamic phase any time soon – it's probably more realistic to think that this would be run in a clinical trial type way – everyone gets randomised to one of the three basic options (this could allow for patient choice if we use point of care randomisation) and we determine which is the better option 'on average', but I'm really just trying to point out how that is still a clumsy design. The problem of stratifying treatment type by characteristics (meth users, age, sex etc) is that we have no regression-type data on which of those variables is associated with different outcomes. But we could get at least some of these data from the initial role out phase…

So that's all a very long way of saying that I think we need to develop this idea as two related but discrete steps:

I) Study 1. We do a predictive type study with the initial roll out of depot – is it right that more meth users stabilise faster/better on depot than non-meth users? Can we identify any other predictors of good treatment outcome on either depot or non-depot? I don't exactly know how to do this (Bruno???), but it's sort of us specifying what we think the uptake of depot will be in practice, and then constructing some sort of algorithm to see how closely the observed data match our predictions. I think that's better then a more simple post-hoc regression analysis because we are forcing ourselves to think this through apriori.

II) Study 2. Based on the findings of this predictive study, we create our treatment 'rules'. We can do that without study 1 (it's important that we can consciously uncouple studies 1 and 2!) but I like the idea of the rules being at least partly based on observational study – seems less like just guess-work (although it probably isn't, really). Once we have our set of treatment rules, we can then design an embedded, pragmatic clinical randomised trial to test the rules and get our D&A clinical system to learn as it goes along about which rules are most effective for most clients (this could be an adaptive trial, or a point of care randomisation trial – I think a standard RCT won't work given clients (I think) will always have the option to say no to a treatment arm in an RCT – one of the features of a pragmatic trial is we want all clients involved, even if that means they choose their preferred treatment option.

III) I'm trying to think through whether we could do this as an individual pathway trial . For example: client A says s/he doesn't care what s/he gets, so client A is randomised to rule 3, we observe the client does not stabilise on rule 3, so we switch her/him to rule 7 (the basis for choosing the new rule could be randomisation or based on some sort of clinical rule based on a clinicians best guess about why the client didn't stablise), the client stabilises on rule 7. So the system should learn that the next person with the same characteristics of client A should get rule 7 first. If that works then it strengthens the weight we give to the idea that clients like client A should get rule 7 – but it needs to be carefully observed to rule out the possibility that client A stabilised because s/he got

rule 3 and then rule 7, not just that s/he stabilised while on rule 7. And so on. But it is very early in the morning here and my head is hurting from jet-lag so I'm about done trying to work this option through (it'll get complex because there are multiple rules and multiple clinical outcomes for each treatment episode – ie, there may be a different rule or combination of rules for successful detox, successful stabilisation, successful maintenance).

AS – Opioid Agonist Treatment study with SVH

Background

- We got a small amount of money ($40k) to do a retrospective, regression type study to see if we can identify client characteristics and features of their treatment that are associated with different (better or worse) clinical outcomes.

- It is very early days, but we had our first meeting and everyone was agreeable to the idea of trying to run this analysis in a way that will lead into a pragmatic trial.

- Really, the idea here is the same as the first idea above, but instead of doing a prospective sort of prediction analysis, it's a retrospective analysis of characteristics associated with better (or worse) treatment outcome.

- In our first meeting we canvassed many of the same ideas as above:

    - Is it ok to define treatment outcome as 2 or 3 clinically meaningful and 'hard/measureable' outcomes: detox and/or stabilisation, then maintenance?

    - We briefly had a first go at discussing the sorts of variables of interest, and we split those into variables that could be manipulated in treatment vs those that can't. Something like this – but it is very early days:

Treatment variables that could be manipulated to test experimentally (after the retrospective observational study)	**Other variables that can't be manipulated in treatment but may be associated with outcomes and therefore guide clinical decisions**
1. Which drug: bup or mmt?	1. Regularity of attending treatment appts
2. Which dose?	2. Other drug use
3. Referral pathways	3. Primary drug of concern
4. Switching drugs	4. ATOP score and (other measures) at intake
5. Switching dose	5. Client demographics
	6. Reason for stopping
	7. Use of other services (e.g. GP)

- Possible outcomes could be defined as:
    - Achieving stability
    - Retention in maintenance phase of treatment
    - ATOP scores
    - Maybe something like less use of acute care (ED)/emergency services

(ambulance)

- Possible data sources:
    - CHIME
    - Methadose (this is moving to idose in the next month or two)
    - Possibly My Health
    - Possible access to medicare numbers or medical record numbers or linked data of some sort
    - Data linked to crime to show reduced involvement in crime

- Could we move to real-time data monitoring/data visualisation to support faster and more accurate clinical decision making?

- There are some of the same issues here as with the first idea: patients like to choose their level of dose and drug. I think I heard the clinicians saying typically clients want to start on a relatively low dose and stay there, whereas clinicians typically want them to start on a higher dose until they stabilise a bit, then reduce the dose over time.

- I think all this patient choice means we really need to develop our skills in point of care randomised trials, and adaptive trials – the idea that it is fine (heaven help us even preferable!) for clients to choose where they start in terms of treatment but perhaps the trick is to really work with clients in helping them see the value of monitoring their progress so we can adapt their treatment where needed. And of course we have to build good quality evaluation around those parameters.

Aims

The key aim for our pragmatic trials group would be to construct a pragmatic trial protocol that would form the basis for a grant to fund the trial.

It would be terrific if we could design something that both SESLHD and SVH (and possibly even SWSLHD), and perhaps some of our rural/regional services, might agree to trial together.