**Project Title:** Guidance on the use of estimands in mental health trials

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**Introduction**

Randomised trials are used to evaluate how safe and effective interventions are. However, trials can address different questions about the effect of an intervention (e.g. the effect if everyone used it as intended vs. its effect regardless of whether some patients do not fully adhere). Therefore, the precise research question being addressed in the trial needs to be clearly described to avoid misinterpretation of trial results.

To ensure that research questions are clearly defined, the ICH E9(R1) addendum was released, which provides a framework for describing estimands. An estimand is a precise description of the treatment effect that a study aims to quantify, and involves specification of 5 attributes: (i) population of patients; (ii) treatment conditions; (iii) endpoint; (iv) summary measure; and (v) strategies to handle intercurrent events, such as treatment discontinuation or switching.

Clear description of the estimand facilitates alignment between study methods (including design, data collection, and analysis) and the research question, as well as evaluation of the research question’s clinical relevance to key stakeholders, including patients, clinicians, regulators, and health technology agency members. Because of these benefits, estimands are now required by numerous medicines regulators, including FDA, MHRA, and EMA, and are becoming increasingly common in academic trials.

However, the ICH E9(R1) addendum was developed for pharmaceutical interventions, and mental health trials may have additional considerations not covered by the addendum, rendering the implementation of estimands in such trials challenging. For example, many mental health interventions are delivered by healthcare professionals, such as cognitive behavioural therapy (CBT) delivered by a trained psychologist. In this setting, the effect of CBT may depend on the psychologist’s expertise, or how closely they adhere to the guidelines on the intervention delivery (i.e. fidelity). Thus, proper specification of these attributes is essential both to properly characterise the study’s research question, and to understand the best way to carry out the analysis and data collection.

However, since these essential attributes are not covered by the ICH E9(R1) addendum, those using the addendum may not be adequately describing their target estimand. As a result, the precise research question their study sets out to address may not be clear, and their study methods may not be fully aligned with their objective, potentially leading to results which are not useful for clinical decision making by stakeholders.

Thus, there is urgent need to provide guidance on what additional considerations are required to implement estimands in mental health trials, to ensure the benefits of estimands are able to be fully realised in these trials. This will enable trials of mental health interventions to address clear and meaningful research questions using appropriate statistical methodology.

**Objectives**

Our overall objective was to develop guidance on how estimands can be appropriately implemented in mental health trials to ensure these trials are addressing clear and relevant questions using robust methodology.

To fulfil this, we planned to:

* Conduct an evidence review to (a) determine whether other previous guidance on this topic was available; and (b) identify any potential additional requirements for estimands in mental health trials
* Hold a 1-day expert panel meeting to reach consensus on what additional items should be included in the guidance for estimands in mental health
* Develop dissemination materials in collaboration with PPI representatives to explain the concept of estimands in mental health trials for stakeholders

**Progress**

We successfully completed the evidence review, the 1-day expert panel meeting, and the main part of the dissemination materials (a video explaining the concept of estimands in mental health trials).

The preliminary guidance developed from the consensus meeting is available in Table 1, along with an example of how this guidance could be applied to a trial of CBT (both in the appendix). We are currently in the process of refining this guidance based on collaborator feedback, and once finalised we plan to write a manuscript and submit it for publication in a peer-reviewed journal. This manuscript will:

* Summarise the evidence review we conducted as part of this work
* Summarise the 1-day expert panel meeting, including results
* Describe the newly developed guidance around using estimands in mental health trials
* Provide examples of how this guidance could be used to describe estimands in mental health trials, and provide brief explanations of each item in the guidance

**Outputs**

The video explaining the concept of estimands in mental health trials has been released, and is available at: <https://www.youtube.com/watch?app=desktop&v=UX8MmPo27rc&feature=youtu.be>

**Future plans**

We will update the guidance based on feedback from collaborators, and then publish this as part of a manuscript for a peer-reviewed journal.

We will also develop additional dissemination materials, in the form of an infographic which explains the guidance for stakeholders.

**Appendix**

**Table 1 – Draft guidance for estimands in mental health.** This table shows the attributes that should be filled out when completing an estimand for mental health trials, as well as some points to consider for each attribute. This guidance is in draft form, and will be finalised based on feedback from collaborators.

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| --- | --- | --- |
| **Attribute** | **Explanation** | **Additional points to consider for mental health trials** |
| Population of individuals | Which individuals or patients are of interest |  |
| Intervention conditions | Which interventions are of interest for the comparison | Does interest lie in understanding the intervention’s effect if delivered remotely or in-person (if applicable)? Does interest lie in understanding the intervention’s effect if delivered 1:1 or in a group setting (and what size of group), if applicable?  |
| Intervention provider(s), if applicable | Who will deliver the intervention(s) | For interventions delivered by a provider such as therapist or social worker, the intervention’s effect may depend on the provider’s expertise or training. Does interest lie in understanding the intervention’s effect if delivered by providers with:* A certain qualification?
* Specific training?
* Certain prior experience or expertise?

If providers are expected to become more skilled throughout the study as they gain experience in delivering the intervention (i.e. “learning effects”), how will this be handled in the estimand definition?  |
| Endpoint | Which outcome is to be used for the comparison |  |
| Population-level summary measure | How endpoints will be compared between intervention conditions (e.g. risk ratio, odds ratio, etc) |  |
| Strategies to handle intercurrent events | How intercurrent events (post-randomisation events which affect the interpretation or existence of the endpoint) are handled in the treatment effect definition | In addition to intercurrent events which occur at the level of the individual (such as stopping the assigned intervention early, or switching interventions), intercurrent events can also occur at the level of the provider (if applicable), e.g.:* Therapists not delivering all modules of the intervention
* Lack of fidelity to the intervention
* Providing additional support, beyond the assigned intervention

The same strategies for individual-level events can be applied to provider-level events, e.g. does interest lie in a treatment policy strategy (the intervention’s effect regardless of whether the provider delivered it as intended) or a hypothetical strategy (the effect if the provider had delivered it correctly)?Individuals may experience different types of intercurrent events for provider-delivered interventions, e.g.:* Switching from one provider to another midway through the intervention
* Lack of engagement with the assigned provider

The same strategies for other intercurrent events (e.g. treatment policy, hypothetical, etc) could be applied.Many mental health trials compare treatment as usual (TAU) + intervention vs. TAU alone, where TAU may be the offer of a standard medication or therapy. Sometimes the uptake of TAU may differ between intervention and control arms, and standard intercurrent event strategies could be applied to uptake of TAU, e.g. does interest lie in understanding the intervention’s effect regardless of any differential uptake of TAU, or if each intervention arm had the same uptake of TAU? Estimands may sometimes be defined based on some measure of adherence, usually if interest lies in understanding the effect in those who would adhere (principal stratum strategy) or if all individuals had adhered (hypothetical strategy). Mental health trials may have additional considerations when defining adherence, including:* Whether adherence incorporates how well an individual has engaged with the intervention
* Whether adherence is based on attending a certain number of intervention sessions (if applicable), attending certain key sessions, or something else.
* For multi-component interventions, which components are included in the definition of adherence.
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**Table 2 – Examples of two possible estimands for evaluation of cognitive behavioural therapy (CBT) on depression.** Both estimands are for the comparison of eight sessions of CBT vs. usual care on depression symptoms (as measured by the Mood and Feelings Questionnaire (MFQ) at 6-month follow-up) in 16-18 year olds who self-referred to their general practitioner with depression. The two estimands differ in their objectives: estimand 1 aims to understand the effect of CBT if it were applied in real-life practice (i.e. regardless of whether it was delivered or followed exactly as prescribed), while estimand 2 aims to understand the effect of CBT if it were delivered as followed as prescribed.

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| --- | --- | --- |
| **Attribute** | **Estimand 1 (Objective: evaluate the effect of CBT if it were applied in real-life practice)**  | **Estimand 2 (Objective: evaluate the effect of CBT if it were delivered and followed as intended)** |
| Population of individuals | 16-18 year olds who self-refer to their general practitioner with depression. | 16-18 year olds who self-refer to their general practitioner with depression. |
| Intervention conditions | Eight sessions of CBT vs. usual care | Eight sessions of CBT vs. usual care |
| Intervention provider(s), if applicable | NHS-based psychologists  | Psychologist with ≥5 years experience who was treated at least 30 individuals with CBT for depression |
| Endpoint | MFQ at 6-months | MFQ at 6-months |
| Population-level summary measure | Difference in means | Difference in means |
| Strategies to handle intercurrent events | Individual stopping CBT early – *treatment policy strategy (effect regardless of whether individual stopped early)*Lack of fidelity by intervention provider – *treatment policy strategy (effect regardless of whether provider delivered CBT as intended)* | Individual stopping CBT early – *hypothetical strategy (effect if individual had completed all sessions)*Lack of fidelity by intervention provider – *hypothetical strategy (effect if provider had delivered CBT as intended)* |