Evidence based trials: How do we make studies within trials routine?

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Studies within a trial (SWATs) are defined as 'studies that would embed research within research, so as to resolve uncertainties about the effects of different ways of designing, conducting, analyzing and interpreting evaluations of health and social care'.[1] Embedded methodology trials are a specific form of SWAT where patients are randomly allocated to intervention or control conditions of the trial process being tested.

Despite the potential of SWATs to contribute to the evidence base on trial efficacy, they are comparatively rare.[2,3]

The recent MRC START programme of research implemented 10 embedded methodology trials evaluating two recruitment interventions in existing host trials.[4] This work demonstrated the feasibility of the approach, but also highlighted a number of actual and potential barriers.

Many of the barriers to SWATs could be addressed through early engagement in a trial's development process, and more significant 'upstream' intervention is required to overcome concerns on the part of investigators and enhance capacity, opportunity, and motivation.[5] We propose that an effective method of increasing engagement among investigators is working with funders and clinical trials units to enhance uptake of methodological work as part of their processes. However, little is known about attitudes among funders and clinical trials units, and there has been no comprehensive assessment of the organisational or policy level barriers and facilitators.

Activities undertaken

Screening survey of all registered CTUs

Interviews with:

- CTU leads
- senior trialists
- trial managers
- funders

Workshops with:

- ICTMC 2015 participants
- UKTMN 2015 conference participants

Webinar with:

- UKTMN members

Methodology

Sample:

- Directors of all CTUs registered at June 2015 were sent a short screening survey and invited to participate in an interview
- Key funders were identified by the research team and other interviewees
- Senior trialists were identified by CTU leads or the research team
- Trial managers who attended the embedded trial methodology workshop at the UKTMN were invited to take part in a short interview
- Two workshops were held, one at UKTMN 2015, one at UKTMN 2015
- A webinar open to all UKTMN members was given in December 2015.

Data collection:

- Interviews were primarily conducted by phone, using a semi-structured interview guide and were recorded and transcribed
- Notes were taken at workshops
- Questions and comments were collected from the webinar.

Aims:

1 map current barriers to the implementation of SWATS

2 identify potential facilitators of SWATS perceived by decision makers in relation to the implementation such as organisational influences and points in the process at which implementation could be supported,

3 develop policies and interventions to strengthen the clinical trials infrastructure in support of SWATs

4 explore the implementation of processes to support SWATs with a partner CTU.

Data analysis:

- Framework analysis using NVIVIO was used to group themes
- The Clinical Trials route map was used to structure comments relating to trial stages[6]
- McKinsey 7S was used as a frame for organising comments about CTUs and the CTU network[7]
- Additional codes were generated for all other comments
- Once initial codes had been identified, findings were synthesised into four themes.

Key outcomes

Data reflecting barriers and facilitators to SWATs were grouped in to four themes:

1 Understanding and acceptance of the need for SWATs to improve the trial methodology evidence base
2 Wider context of trial development and funding
3 Specific stages of trial development, implementation and delivery
4 Organisational aspects of CTUs and the CTU network structure.

1 Understanding and acceptance of the need for SWATs to improve the evidence base

- Recognition of the need for embedded trials and SWATS to improve the evidence base on trial methodology was well established amongst CTU leads, senior trialists and trial managers.

  "For at least 50 years people have struggled with the idea of making trials as efficient as they can be in a lot of different ways… and they still are… clearly things are not improving in the way that we think they should."

- However, recognition was not seen to extend to the wider research community where Chief or Co Investigators and other trial management group members were frequently cited as barriers to implementing SWATs.

  "I did put in a section [on the application] saying we are going to do an embedded trial, but all the other applicants thought this was a distraction and wanted me to take it out, which I did."

Funders too acknowledged that:

  "it has been difficult to stimulate many of the research community in to this area."

Concerns arose from:

- adding complexity to a trial
- lack of equipoise about the intervention/belief in a particular methodological approach, or
- fear of reducing recruitment in one arm
- whether SWATs are an appropriate methodology.

Potential facilitators included:

- Good working relationship between the CTU and CI
- CTUs making inclusion of a SWAT conditional for accepting a trial
- Continued promotion of and dissemination about the need for SWATs.

2 Wider trial development and funding context:

- Access to funds was seen as the key barrier, cited by virtually all researcher interviewees. Primarily, none of the existing funding streams are seen as open to SWAT research
- There was recognition amongst funders that this has previously been a gap in funding
- In direct contrast to researcher views however, policy funder views reflected a more positive and evolving approach to funding methodological work including:
  - two NIHR calls with options for 'methodological bolt ons' (although the future of this approach is undecided) and
  - the broadening of priorities in the MRC methodology research programme to encompass more recruitment and retention focused methodological work.
- There was some indication that, within mainstream NIHR funding, applications for embedded methodology trials as part of a full trial could be considered 'in scope', particularly where:
  - equipoise over best recruitment or retention methods in the main trial have been established
  - the embedded intervention uses an adaptive trial design with analysis of recruitment or retention data at agreed points (eg at the end of the pilot phase)
  - plans are in place for all participants to switch to the optimal recruitment or retention arm where an effect is demonstrated.

Other funding barriers to implementing SWATS were identified as:

- timescales and pressures within the funding cycle
- downward pressure on cost and the need to strip out any 'extraneous' costs
- reducing the competitiveness of a bid.

Potential facilitators included:

- clarity from funders about what is 'in scope'

- development of 'off the shelf' interventions
- development of low/no cost interventions (such as the IQuaD retention intervention currently promoted by Trial Forge).[8]

3 *Specific stages of trial development, implementation and delivery*

Comments were primarily focused on the early stages of trial development, the points on the route map up to the start of recruitment.

- Moving from support for the principle to idea generation for a specific SWAT was one area of difficulty:
  - What to embed – what constitutes a worthwhile intervention?
  - Which trials to embed in – what makes a good host trial?
  - At what point should the idea of a SWAT be introduced?

Potential facilitators were cited as:

- Sharing of research ideas (as through the SWAT repository) and experiences, possibly through formal co-ordination of efforts around a specific research question such as in Trial Forge or MRC START.[9,6,4]

  "the Trial Forge idea … it's coordination and collaboration. The first bit is that coordination, it's what should we do? Again that removes a barrier if you can say, well, here … is the thing to do. It removes a barrier, you just make a decision: do I want to take part or not? You haven't had to dream the thing up."

- There was particular support for setting an agenda for research priorities and co-ordinating efforts to ensure maximum impact
- Host trial characterstics, stage of development and level of service provided by the CTU were seen as interrelated criteria in determining suitability to host a SWAT, with SWATs seen as more feasible where:
  - CTUs provide a full trial service, and
  - Are involved in the design and development of the trial from an early stage.
- The potential value of protocols and tools to support the implementation of a SWAT was also recognised.

Concerns were raised about external review as a part of the funding or ethics process these included the potential for the SWAT to:

- Cause confusion or detract from the main trial
- Generate objections that undermine the full application or delay its implementation

- For ethics there were particular concerns where SWAT methodology might diverge from standard RCT practice for example:
  - No pre-notification of participants in recruitment trials
  - The relevance of a power calculation for the embedded trial (particularly where a meta-analysis is planned).

The main facilitator identified here was the need for clear direction from funders and NRES about how SWATs should be considered within a full trial application.

Other barriers in the trial delivery process were identified around:

- Trial initiation and the feasibility of any SWAT that added to the burden of set up
- Monitoring and implementation fidelity of the SWAT, particularly on large multi-site trials
- Ownership of the embedded trial research and data.

However, these types of issues largely mirror the challenges found within all trials work. Resolving these problems was seen as much more within the remit of CTUs.

4 *Organisational aspects of CTUs and the CTU network*

Data relating to CTU organisations and the network were grouped according to the McKinsey 7S model which identifies seven broad aspects of organisation important in change implementation.[7]

Strategy : *plan or course of action leading to the allocation of an organisation's finite resources to reach identified goals*

The potential of SWATs to contribute to CTU strategy was recognised in a number of key areas:

- Increasing unit capacity
- Developing staff
- Increasing methodological work and
- Increasing publications.

The extent to which SWATs formed part of CTU strategy varied considerably and enacted strategy was evident in only a few units:

  "Well it's across the board, we try and do it on every trial… "

  "Okay, well we've been thinking about it for a long time because we're obviously aware that other people do it, and some people get a lot of papers out of it, and also it's a potential for trial managers or trial staff to get their own papers to lead on a paper and be a first author. So we think it's a good thing, and also one of our other objectives is to do more methodological work."

There was also widespread recognition of how the CTU network could be used to facilitate greater strategic commitment to SWATs, from encouraging other CTUs to undertake the work, to more structured agenda setting exercises and formal collaborations to deliver SWATs. However, although the expertise clearly exists, the operating pressures within CTUs and the other barriers identified in relation to SWATs, make such developments unlikely in isolation.

Staff: *distinctive capabilities of key personnel, how grown and developed, and* **Skills**: *the organisation as a whole*

CTUs varied in the extent to which staff group membership was clearly defined, however the skill profiles described by CTU leads were broadly similar with core staff including statisticians, methodologists and trial and data managers. Running SWATS was felt to be well within the existing CTU skill set, both in terms of individual and organisational skills.

Structure: *Who is in charge, how are decisions made, authority relationships*

CTU leads described similar decision making structures with a board or senior management team assessing each proposal and making a decision on support. However, decision making power does not necessarily sit with the CTU in relation to a SWAT. This affects units' ability to make direct decisions about implementing SWATs, in particular trial where the CTU is dependent on a receptive CI.

Style: *How key managers behave in order to achieve the organisations goals*

Although few CTUs were consistently implementing SWATs, the importance of knowledge sharing was thought to be paramount here. In particular, the role of a champion (not necessarily within each CTU, but easily accessible to staff on an ongoing basis) was seen as a strong potential facilitator.

Systems: *procedures and routine processes*

The nature of trials work means that CTUs have high levels of expertise in developing and implementing systems and offer great scope for routinizing the delivery of SWATs. However, at present, these systems don't exist in a formal way. Additionally, because most SWATs have been conducted in an ad hoc way to date, there is little shared learning on what processes or approaches might work best.

Looking at existing systems and identifying where SWAT elements could be included was felt to be a straightforward process for CTUs, but seen to be a minor consideration in relation to the other barriers faced.

Implications

1 There is a perceptual gap between funders and researchers about the funding available for SWATs. A number of simple actions could remedy this:

- Greater clarity from funders about the status of SWATs in the funding process
- Wider communication of the expectation that trials should aim for evidence based recruitment approaches.
- Actions that send clear signals to CIs/trials teams and beyond about support for embedded methodology trials (eg space on application forms)
- Greater engagement between CIs, methodologists, CTUs and funders to discuss SWATs prior to the submission of a bid
- More innovative design from trials teams when incorporating SWATs.

2 Existing arguments for SWATs tend to focus on the lack of evidence per-se and that they are a good thing 'in general'. We need to develop more nuanced arguments to support the adoption of embedded trial methodology, particularly around:

- Much clearer expression of the synergy between the host trial and the SWAT. This could include addressing particular factors around recruitment for that type of trial/population; and an adaptive trial design, with clear indication of how/when a main trial will review recruitment data and switch to preferred recruitment method.
- Clearer articulation of the potential contribution of SWATs to efficient trial methodology.
- Clearer strategy within the trials community in relation to embedded methodology trials:
  - Consensus building exercises about intervention priorities
  - Collaboration between a number of CTUs to promote and implement interventions with a specific evidence goal in mind, or
  - Efforts from an individual CTU to promote and implement an intervention over a number of trials with regard to a specific recruitment process or a specific recruitment question.

3 From an organisational perspective, although trialists and CTUs are well equipped (in terms of skills) to implement SWATs the processes are often poorly understood or have yet to be given consideration. Additionally there are areas where SWAT methodology diverges from standard RCT practice (eg the need to inform participants of their involvement in a trial, the importance of a power calculation for the SWAT). Various materials exist via current initiatives such as the SWATs repository, MRC START and Trial Forge that could form the basis for a set of guidelines for running embedded trials.

Next steps:

1 Dissemination of the summary report to relevant stakeholders
2 Preparation of a paper for an academic journal
3 Dissemination of findings at appropriate conferences
4 Ongoing exploration of the implementation of strategies and processes identified to support SWAT implementation with our partner CTU

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