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THE DESIGN OF CLINICAL TRIALS AND ITS ASSOCIATED SUPPORT SYSTEMS IN INTERPLANETARY MISSIONS – A THOUGHT EXPERIMENT AND CREATIVE WORKSHOP

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Abstract

On Earth, the best available evidence to inform decisions on the effectiveness of treatments are randomised controlled trials. Depending on relevance of the question, availability of resources and willingness of individuals, these trials range from a few people to thousands. These trials are usually repeated across the world on different populations which provides further information on the generalisability of the effectiveness of interventions. Only a fraction of individuals on Earth participate in clinical trials to provide the evidence basis for the larger population. In aerospace medicine, the number of astronauts is quite limited so doing large clinical trials is difficult: the evidence in aerospace medicine primarily relies on simulated studies on Earth which may be randomised controlled trials or small case series with astronauts in space.

The current discussions on long term missions to Mars and other planetary exploration, raise the question of what is the ideal approach for building an infrastructure to conduct clinical trials for long term interplanetary missions. Long term missions require the continuous commitment and motivation of participants in the clinical trial, therefore patient involvement in the research process is more important. This paper uses a combination of a thought experiment with a creative, simulated and interdisciplinary workshop to build a conceptual framework on how clinical trial research infrastructure can be innovated in an inter-planetary mission. Some key aspects of the framework includes: a) Designing and prioritising interventions to manage the problem (democratic versus management approach) b) Overall design of the research project (applicability of prospective meta-analysis, patient preference trials, N-of-1 trials) c) Allocating participants to groups (stratification not only based on characteristics but also by roles and job specification, using Bayesian randomisation to allocate individuals into groups and patient preferred trials) d) Outcome selection and data collection (identifying biomedical, clinical, patient-related, performance-related outcome, data collection over time and monitoring need for adaptation and change) e) Ethics and Partnerships (ethics and consent issues and how they relate to partnerships and relationships). We will suggest using the same methodology to facilitate more in-depth discussions on certain aspects of a clinical trial or managing a diverse range of health problems *e.g.* contagions.

Keywords: interplanetary mission, clinical trial, evidence-based healthcare, medical simulation

This paper outlines a thought experiment in collaboration with artists, designers and technologists to develop a creative workshop that used a combination of a virtual reality, simulation set-up and perception-oriented art piece with a facilitated discussion. It reports the methodological and implementation issues with regard to clinical trials in interplanetary missions following the experiment and workshop. The results attempt to challenge how we construct and work towards the future of medical research in interplanetary missions. It also intends to provide a structure that can be used to engage a wider audience in discussions on innovation in clinical trial methodology on Earth.

1. Introduction

Popular science fiction movies can shape or influence our imagination for future but do not engage all aspects of medical research development. For example, the Qualcomm Tricorder X-prize has been awarded to a family-led team to develop a medical device that intended to develop technologies to diagnose a set of 13 medical conditions independent of health professionals or facilities and continuously measure five vital signs in 2017. The idea was inspired by the popular science fiction series Star Trek. In the Star Trek series and similar sci-fi movies and series, a doctor uses complex

technologies to make very accurate diagnoses (through micro- and nanotechnologies, data and information) and often finds a treatment to cure the problem/disease (in lots of cases to total health without adverse events). In this and similar popular sci-fi movies and series, the storyline emphasizes the increasing accuracy of diagnostic technologies and the skill and genius of the doctor. Less attention is given to the possibilities of using innovative clinical trial research methods in interplanetary missions. The conundrum of clinical trials in interplanetary missions and the scenario explored in this thought experiment has a lot of similarities to the historical scenario of sailors affected by scurvy on navy ships in the 17th century. The standard method of proposing medical treatments (skilful and smart doctors suggesting treatments based on experience) generated several possible treatments for scurvy. However, there were still uncertainties as to which treatments work best to treat scurvy. The mortality and morbidity of scurvy between sailors was still high. James Lind was a navy doctor who trawled the literature and anecdotal advice on treatments, and then conducted a small controlled clinical trial to identify an effective treatment. The latter provided the evidence to combat the existing conflict and uncertainty (1).

There is a need to reconceptualise clinical trials in interplanetary space missions because of how potentially different conditions would be between living on Earth and settling on other planets, *e.g.* Mars. These include physical aspects such as partial gravity or a different atmosphere, along with the psychological and social issues of small and isolated populations. The small and isolated community can be simulated with smaller numbers of humans; however there are other challenges with regard to the relationship between individuals, patients, clinicians and trials that introduce new problems. Moreover, the risk of the decisions and their consequences has different implications that can affect the decision-making process.

The issues in relation to clinical trials in such missions are multifaceted. If interplanetary missions will go forward, it will be a smaller of population living in micro- or partial gravity. These will be the only individuals who have direct exposure to the environment and can be potential participants of clinical trials. Data collection in a clinical trial is time consuming and requires further administrative steps to clean the data, process and manage them before the evaluation and analysis stage. Any mission will have limited resources with regard to supplies and access to technology. Therefore, evaluating all healthcare interventions or health-related lifestyle choices will not be logistically feasible. Finally, if there is a health problem, the people involved in the mission will both be part of the planning mission, the people who require treatments and only potential subjects to be part of an experiment. There has been no example that we are aware of (in space or on earth) in which a community was democratically involved in designing a medical research methodology *and* were the subjects themselves.

On Earth, most people are never involved in a clinical trial during their lifetime. Due to the large population of Earth, each of us can rely on the research that has been conducted on other individuals. The combination of clinical trials on a selected sample of population, the data from regularly collect patient records, and *in vitro* and animal studies—along with the experience of the clinicians—provide the underlying evidence to inform healthcare decisions. In contrast, the evidence currently underlying aerospace medicine research is predominantly based on case reports of astronauts when they are in space, a follow up after they came back to Earth, or simulation studies on Earth such as bed-rest studies. There is lots of research on creating an enhanced simulated space environment (or aspects of the space environment) on Earth. The enquiry that we want to explore is how to build clinical trials over a series of space missions that could gradually approach the necessary sample size and how the clinical trial can be built to be consistent with social, political and organisational issues of a space mission.

2. Material and methods

The project included three steps:

- a theoretical thought experiment in which we explored how we can increase the sample size using different methodological techniques and re-conceptualising partnerships between clinicians and trialists and the patients in organising the study.
- Two creative workshops to engage a wider audience in the thought experiment.

The primary theoretical thought experiment is a space mission with 40-50 people on Mars. We selected a non-contagious disease, similar to the scurvy scenario, to explore in this experiment. The trialist/clinician gets increasing reports of incidence of eye problems and vision disturbances and needs to find an intervention to manage it. The scenario asks the participants to draw a diagram to demonstrate how to set up, design, implement and maintain a clinical trial. The idea is that it is important for the trialists to not only manage the situation but also to set up the best way to implement and evaluate the healthcare situation so that it produces high quality evidence for this mission and future ones. The scenario is based on recent reports that some astronauts experience vision impairment that can last for

a long time during space missions(2). The participants received quotes from astronauts *e.g.* a quote from astronaut Mike Baratt – "*It's my right eye that has apparently been permanently remodelled*"(3) (Table -1).

The first workshop was run in Torbay Hospital. It included a combination of an immersive and interactive session along with a facilitated methodological discussion. The immersive part built on previous research on eliciting audience participation by providing a restrictive environment like a space mission rather than relying solely on the pictorial realism of the depiction of space. It included a virtual reality demonstration of a Soyuz spaceship leaving Earth followed by a simulation of a spaceship accident. The latter was not intended to be realistic; it attempted to demonstrate some limiting aspects of a space mission. It included an individual in a fat suit, tinted glasses and big gloves who was supported by suspension bands and could move around (Figure 1 - **Preparing for the simulation**). A second individual was present who was immobile and non-communicative and dressed in a Biohazard decontamination suit. The room had limited lighting. There were people in the room and some outside the room watching through a monitor (Figure 2 - **People watching and advising the situation from the control room**). There were clear problems with communications and only certain people could talk. The simulation was of a post-accident scenario where an astronaut had to attempt to rescue an injured colleague. Due to damage to the communication equipment the remainder of the crew could only receive and pass information via mission control (simulated by the team in the sim suite control room) and direct their colleague. During the debriefing, the participants discussed the challenges dealing with the limitations of the situations. They usually started to follow their standard emergency medical procedures and did not consider that it might not be applicable to the unusual situation. As part of the immersive experience, we also gave them an opportunity to use an optical piece develop by Terry Pope (the hyperscope and the pseudoscope) to experience hypothetical changes in position of eyes and its impact on vision (4). The immersive part was followed by an interactive discussion where participants worked through the scenario used in the thought experiment.

Figure 1 - Preparing for the simulation

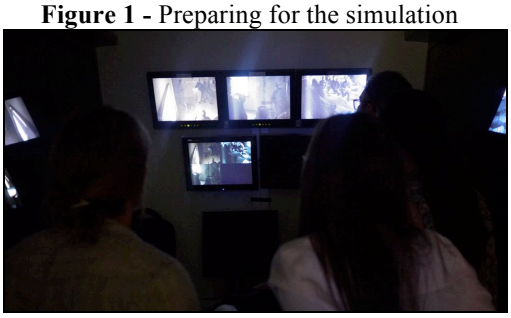

Figure 2 - People watching and advising the situation from the control room

The second workshop was conducted as part of an evidence-based research workshop at the Cochrane Colloquium, Edinburgh. The workshop did not include the immersive session and only included the interactive discussion. The participants were against asked to draw diagrams. The main difference was that the first workshop predominantly included doctors/consultants along with a few scientists and the second workshop included patients and patient advocates along with clinicians and methodologists. The second workshop also emphasized the applicability of the discussions to re-conceptualising the conduct of clinical trials on Earth.

Table 1 – Mars case scenario given to participants of the workshops

Item	Explanation
Case scenario	In a mission to Mars, there are 40-50 people who are staying on that planet for three years. You have increasing reports of individuals having differing eye problems *e.g.* blurriness, seeing spots, problems in seeing distance, *etc.* These eye problems are affecting the ability of individuals to perform their duties and affecting the mission in general. Moreover, it causes anxiety and stress as other members of the mission are worried that they might become affected. You need to come up with a solution to manage the situation and determine how to conduct clinical research that not only supports this mission but future ones.
Discussion guide for participants	• How do individuals come up with potential interventions and prioritise them that could be used in clinical trials? Who do they involve in the decision-making process? • How do they make decisions about what data to collect in order to evaluate the effectiveness of the interventions? Encourage people to think about clinical outcomes, biochemical and pathological outcomes along with performance outcomes. The latter is important for the mission, the former important for future missions. • If people are familiar with clinical trial methodology, encourage them to think about ideas on how they would change the allocation, blinding or other aspects of the clinical trial. • It will be helpful to encourage people to think and discuss ownership of clinical trials and the relationship of individuals in the mission with the leaders of the mission and how it can affect the social dynamic of the mission.

4. Discussions

The issues and concepts identified as part of the thought experiment and workshops can be categorised as follows:

a) Designing and prioritising interventions to manage the problem (democratic versus management approach).
b) Overall design of the research project (applicability of prospective meta-analysis, patient preference trials, N-of-1 trials).
c) Allocate participants to groups (stratification not only based on characteristics but also by roles and job specification, using Bayesian randomisation to allocate individuals into groups and patient-preferred trials).
d) Outcome selection and data collection (identifying biomedical, clinical, patient-related, performance-related outcome, data collection over time and monitor its need for adaptation and change).
e) Ethics and partnerships (ethics and consent issues and how they relate to partnerships and relationships).

Designing and prioritising interventions to manage the problem

Astronauts have a lot of training and experience in conducting experiments and collecting data as part of a daily routine in space missions and we expect that most people who are sent on a mission are selected based on those personal traits. However, this becomes more complicated in long-term missions where people face isolation and separation from family and if the mission involves different space agencies, they might have different selection and training criteria, different cultures (both organizational cultures and country and ethnic culture) that might demonstrate differences in a long-term mission more prominently. This can become more complicated if part of the objective of the mission is to build a community on another planet. Therefore, it becomes more important to have a more collaborative and inclusive approach in selecting the research questions that become the priorities for investigation in clinical trials in such missions. This has been recognised by funders and researchers nowadays and there are increasingly more countries for which patient and public involvement in setting priorities for research is a key component of their process – although the quality of the engagement is variable (5).

In the example of public involvement in the work of funding agencies, the people who are involved in setting priorities are not necessarily the same people who will be recruited in the clinical trial itself. There has been no example that we are aware of in which a community was democratically involved in designing a medical research methodology *and* were the subjects themselves. One aspect that can be evaluated, if such a project is implemented, is to get a better understanding on the impact of evolving priorities of individuals in this process. Long-term Antarctica missions can be a potential environment to pilot and evaluate such strategies. In addition to this, we will plan to explore and evaluate using different strategies to democratically

engage with the public in prioritising research questions about the effect of their own health in their communities and how to support these discussions.
During the workshops, there were different approaches suggested to deal with this decision:
(a) Democratic approach to rank the interventions.
(b) Approaching the manager of the mission or the leader that people listen to.
(c) Build a committee comprising of key individuals to make the decision.
The process not only depends on individual needs and values but also the expectations, values and prior agreements from the mission. One example that was discussed in the workshop was that individuals coming from military background might differently react than those coming from academic background.
The social and political impact of the clinical trial on the community has been discussed. These impacts might influence individuals' involvement in the research project and even the design of it. For example, certain expected adverse events from the treatment or consequences of the disease might lead people to prioritise certain interventions. The emergence of these effects can also affect the compliance of individuals throughout the trial.

The overall design of the clinical research project on Mars:

One of the biggest challenges of aerospace medicine research is the low sample size as the number of astronauts is limited. This is also the case with simulation studies. Due to the technical requirements and costs, the number of individuals that are recruited in the clinical trial is limited. Systematic reviews with meta-analyses have been used to synthesize the data across clinical trials that increase the power and generalisability of results. However, they are limited if the clinical trials are too diverse to be synthesized together. There is a possibility to address this issue using prospective meta-analysis which requires that the space agencies plan the clinical trials keeping in mind the future meta-analysis in which the clinical trial will be included. In this way, they could also plan those clinical trials over several space missions especially as a health issue will probably come up again and again in future missions with new individuals (6).

Regarding the eye problem, in some cases we might not able to treat the problem and might need to find ways to ensure that the individuals manage symptoms to be able to perform their duties or live their lives. In these cases and these types of treatment, N-of-1 trials can be useful so will be helpful if individuals have access to ways to incorporate these trials in their daily life (7).

Allocate participants to groups

Clinical trials usually involve randomisation to the group. We sometimes stratify individuals in the groups based on other confounders to explore their impact on the effectiveness of the intervention. During the workshop, the issue was raised that each person has a critical role in the mission. It's important that if the performance of the individual is negatively affected by the trial (either that the intervention does not work or the intervention has problematic side effects), that people with similar roles and job specification would not be in the same treatment group. Another reason for not having people with similar roles or similar living or working places to be in the same group is the possibility of contamination between groups. In these situations, one could implement a stratified randomisation to separate them in allocating them to groups. Moreover, the investigator could use a weighted/unequal randomisation which is still randomised but results in fewer participants allocated to the experimental group (or non-experimental group whichever is deemed to have adverse consequences)(7).
Except to the clinical trialist, randomisation is generally an unusual concept. Although we would expect that astronauts on a space mission would have received training on the issues that are relevant to them, this concept might be still unusual and strange to certain people, especially if they have a health problem that can cause anxiety. There are alternative methods to designing the clinical trial can be used, such as patient-preferred clinical trials, or different approaches to randomising people to the groups, such as Bayesian randomisation.

Outcome selection and data collection
In both workshops, people raised the issue that not only would clinical and biomedical outcomes need to be collected, but also patient-related outcomes and performance-related ones (what people care about). They do suggest that trialists and members of the community should work together to define the most important outcomes for the clinical trials. There was also a discussion on unexpected outcomes *e.g.* unexpected side effects and the need to record and identify them. Some even suggested that we would collect data on each member's personal log (which does raise ethical and consent issues).
During the workshop, people raised concerns about a set of pre-defined and fixed outcomes at the beginning of clinical trial. This is important to provide relevant comparison; however, people's priorities on what the most important outcomes are might change over time. Therefore, it has been suggested that the clinical trial team should have continuous discussion with

individuals in the group to see how the outcomes evolve over time.

Ethics and partnerships

The importance of partnerships, relationships and transparency has been raised. It is key to maintain the partnership and relations with the subjects throughout the clinical trial. The workshop participants also raised the importance of implementing of the results of the trial in the same population, people need to see the benefit of doing clinical trial to take ownership of it. At the end of the workshop in Edinburgh, we asked people how the discussion affected their views on conducting clinical trials on Earth and this was one of the key aspects that they highlighted. The reality that the trial participants are also the trialists' community, colleagues and the patients made the participants of workshop re-think how they approach designing the clinical trials. This is specifically interesting considering the ethics of conducting clinical trials in developing countries, for example the outsourcing the commercial clinical trials to Latin America (8).

There were lots of discussion on challenges of randomising people to one treatment group and one control/placebo group, especially if the intervention is co-designed with the participants and there is a level of anxiety to the eyesight loss or adverse effects of the treatments. Some argued that people who sign up to such missions would be expected to have agreed to these types of experiments. However social interaction, especially in difficult, complicated and stressful situations (loosing eyesight can cause anxiety and stress), evolves in unpredictable ways and it is important to consider how that affects people. Others suggested if individuals are involved in designing the clinical trial and selection of intervention, they are more likely to accept the failure and adverse events. There were suggestions on the need to design appropriate placebos for such clinical trials.

5. Discussions

Although aspects of the thought experiment could have been predominately explored in a logical and narrative way, there are other social and behavioural issues that require participation of a wider audience to identify and unpick. The creative workshops provided a helpful approach to achieve this.

Participants of the workshop found the interaction useful, not only to come up with new approaches to design clinical trials for interplanetary missions, but also to re-conceptualise clinical trials on Earth. there was a realisation that coming up with new approaches was derived from their evolving understanding of the physical environment and the extent to which their training formed their thought processes.

6. Conclusions

The creative, simulated and interdisciplinary workshop provides an excellent vehicle to implement the thought experiments.

The combination of the thought experiment and two workshops identified five aspects that clinical trials would be run differently in this environment:

a) Designing and prioritising interventions to manage the problem (democratic versus management approach).
b) Overall design of the research project (applicability of prospective meta-analysis, patient preference trials, N-of-1 trials).
c) Allocation of participants to groups (stratification not only based on characteristics but also by roles and job specification, using Bayesian randomisation to allocate individuals into groups and patient preferred trials).
d) Outcome selection and data collection (identifying biomedical, clinical, patient-related, performance-related outcome, data collection over time and monitor its need for adaptation and change).
e) Ethics and Partnerships (ethics and consent issues and how they relate to partnerships and relationships).

We will suggest using the same methodology to facilitate more in-depth discussions on certain aspects of a clinical trial or managing a diverse range of health problems *e.g.* contagious ones or the datasets to reflect the issues identified in this exercise.

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