DANISH NATIONAL
CENTER FOR ETHICS

Guidance on decentralised clinical trials (DCT)

Danish National Center for Ethics // Section for the Medical Research Ethics Committees

Version 1.0

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Contact information

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Preface

Assessment of ethical soundness has always been a cornerstone of the proper conduct of clinical research. Research ethics ensures a stringent focus on the well-being of the participant throughout a trial and aids in keeping high scientific standards to obtain information of high quality for the benefit of future patients and society. Denmark has always been at the forefront of developing the necessary infrastructure to evaluate research ethics in clinical trials, which is underscored by the establishment of a national ethics committee system already in 1980.

In the more than 40 years that have passed since, the scope and complexity of clinical research have changed considerably, as have the expectations of the population with regards to how flexible activities of the daily life, including participation in clinical research, must be. The recent coronavirus pandemic has further exacerbated this movement by putting significant restrictions on the mobility of the population with negative consequences for clinical trial participation.

Adapting clinical trials to include more activities away from the research sites has been one way of solving this issue. The umbrella term for this concept is *decentralised clinical trials* (DCTs) and describes how trial activities, like monitoring of physiological parameters, blood sampling, and reporting quality of life, can be performed in the participant's own home or at smaller sites nearby. This decreases the number of necessary follow-up visits at primary research sites, amounting to less burden for the participant in following the trial scheme. There has also been a growing desire to decentralise activities that are quintessential in terms of research ethics evaluation, namely the processes of recruitment and informed consent.

As such, DCTs put a demand on the ethical committee system to rethink the model of what is considered the gold standard for how to obtain consent based on sufficient information about the risks and benefits of participation. A revised model will have to balance the new opportunities of clinical research, introduced by the concept of DCT, with well-known ethical principles for research, e.g. the principles of autonomy, beneficence, justice, and trust, including practical considerations with respect to ensuring that a participant is well informed, comfortable, and safe throughout the trial period.

This guidance provide a description of classical ethical principles known from the current research ethics evaluation applied in the context of DCTs to assist investigators and sponsors in making qualified ethical considerations regarding their clinical trials. The focus is on DCT topics with particular importance to the interface between the participant and investigator before, during, and after the clinical trial. These include

recruitment, informed consent, media, and data processing. Since the guidance is a living document subject to continuous updates, this list of themes may expand over time. Furthermore, this document should be considered the Danish Medical Research Ethics Committee's position regarding the ethically sound conduct of DCTs and seen as complementary to The Danish Medicines Agency's guidance on the implementation of decentralised elements in clinical trials with medicinal products.

Background

Decentralised clinical trials (DCTs) are trials that take place outside traditional research sites, such as hospitals or laboratories. Instead, DCTs take place in the participant's own home, at general practitioners, or at local pharmacies. Enabling such a transfer of trial-related activities is to a large degree dependent on technologies such as telecommunication, wearable devices, sensors, and smart phones. This transfer of trial activities is also similar to the recent developments in telemedicine, which has seen a surge in interest and use over the past decade in the Danish healthcare system, especially with respect to monitoring patients with chronic diseases. However, while implementation of telemedicine, and, in effect, decentralisation of healthcare activities is a continuous and prioritised task with respect to treatment and long-term follow-up, decentralisation of research-related activities has not yet seen the same progression. In addition to this, there is little high quality evidence available to inform about which situations or indications that are of particular relevance for DCTs, although from a theoretical point of view some fields like dermatological and chronic metabolic diseases have been suggested as a rational starting point.

Advantages of DCT

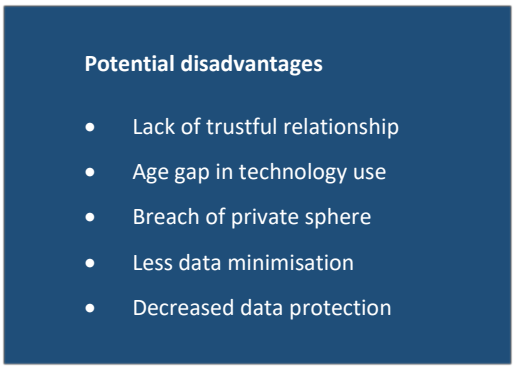
Potential advantages

- Increased flexibility
- Demographic diversity
- Geographic diversity
- Lower costs and variability
- Frequent follow-up

There are several potential advantages of decentralising few or several activities related to a certain trial, examples of which are described here. First, it may be possible to increase the demographic composition of participants, including a broader range of ethnic backgrounds, better gender balance, and reaching subgroups that are less inclined to participate in clinical trials. Second, by decentralising trial activities and decrease mandatory visits to the primary research site, it may be possible to increase the geographical diversity, and allow people that live far away from large medical centres and research sites to have true equal access to participation compared to those living in close proximity. Third, by being less dependent on a large number of investigators and having few experts performing all participant evaluations through remote assessment, it may be possible to both reduce the cost of the trial and decrease variability in the resulting trial data. Fourth, the use of a range of technological devices throughout the trial, especially a high frequency of videoconferencing, may allow the investigator increase the amount of follow-up to ensure the safety and well-being of the participant. Moreover, this may substantially decrease the burden of bothersome travel for ill participants.

From an ethical point of view, several of these potential advantages pertain to relieving burden from the participant and ensure safety, which one should always strive for when designing clinical trials. In addition, the potential of increasing diversity among trial participants in situations where trial populations normally do not reflect the downstream patient population well may increase generalisability of the results and contribute to better scientific quality.

Disadvantages of DCT



There are also a number of potential disadvantages, which are important to consider when decentralising trial activities, especially in relation to informed consent, examples of which are described here. First, with much fewer investigators and personnel connected to the study and in-person visits performed there may be less time to build a trustful relationship between the investigator and participant. This trust is an important factor in the decision about whether to participate in a clinical trial. Although it is difficult to measure trust directly, field studies are yet to be done to determine how a potential loss is in fact a problem to the participant, and how it might be mitigated. Second, there could be differences in acceptance and compliance with technology across different generations, which may show both in terms of lacking knowledge regarding the platforms, where the trials are advertised, and less security in performing trial activities. This might put elderly people in an unfavourable situation with respect to access to participating in DCTs due to overwhelming amounts of follow-up being dependent on the participant instead of an investigator at the research site. Third, there might be a breach of the private sphere, if home visits are required for delivery of drugs or devices and more complex monitoring procedures performed by nurses or physicians, or if frequent videoconferencing exposes private information about the participant's home environment that are of no relevance to the trial. Fourth, there is a risk that continuous monitoring of study endpoints including participant reported outcomes violate the principle of data minimisation in clinical trials. This is a particular issue if there is no high quality evidence to support the relevance of such monitoring compared to classical follow-up at the research site. Fifth, the frequent communication and transfer of health data from the participants' electronic devices to data clouds or physical serves at central research sites may be prone to privacy breaches. General data protection is therefore more of a concern for DCTs compared to their classical trial counterparts.

From an ethical point of view, many of these disadvantages revolve around important aspects of trust, privacy, and equal access to trial participation, all of which are key to ensure enrolment in the trial and generalisability of the resulting data. It is therefore a necessity to develop mitigation strategies, although they might differ substantially. While the existence of an age gap with respect to the use of technology is an issue that might be resolved naturally within few years, the issue of trust may need to be handled with other means. Such means should investigate if the current level of trust in clinical trials can be maintained in DCTs, and if not, whether a new take on trust in clinical trial participation is sufficient in an era of more technology in general and in DCTs particularly.

Research ethics and DCT

Despite having lists that highlight the advantages and disadvantages of performing DCTs in a general context, it is noteworthy that the DCT concept is not an all-or-nothing phenomenon. Because clinical trials already are a composite of large numbers of sub-activities, it is reasonable to substitute one or more activities of the clinical trial for a decentralised version if it makes sense under the given circumstances. Such trials, which decentralise only parts of the original protocol, are termed 'hybrid trials' and are likely to constitute most of the implementation of DCTs. This level of flexibility may enable future DCTs or hybrid trials to focus more on the preferences of the individual, thus benefiting both the satisfaction of participating and the level of retention in the trial. In addition, because the DCT field is still young, there might be a window of opportunity for sponsors and investigators to be proactive and let the ethical principles take centre stage in defining how to conduct a proper DCT. This could amount to more careful and detailed considerations about the ethical soundness of a specific trial submitted to the ethical committees. It could even amount to an increase in transparency by subjecting protocols or ongoing trials to evaluation by stakeholders outside of the regulatory system, e.g. experts in ethics or patients with the disease in question.

The following is a set of non-legally binding recommendations aiming to promote ethically sound DCTs. The prevalent use of the term *should* therefore pertains to moral reasons and not to legal documents. These recommendations are guidelines grounded in basic normative principles applied to the context of DCTs. None of these principles will be treated as ultimately superior and all of the derived recommendations will be treated as defeasible by competing considerations in light of proper argument and justification.

The aim of these recommendations is thus not to provide a simple recipe for research ethics in the context of DCTs. The diverse nature of clinical trials and the moral complexities of doing research do not allow for easy manuscripts, and doing ethics is at least in part a matter of balancing different concerns. This also holds for DCTs. What the recommendations do aim to provide, however, is considerations that will hopefully

improve ethical reflection on various decentralised elements, provide for better studies, promote a common ethical language, and improve trust between participants, researchers, and ethical committees.

Basic ethical principles

Like clinical research in general, DCTs can be analysed and discussed through a range of basic ethical principles. For the present purpose, the principles of autonomy, beneficence, non-maleficence, justice, and trust have been selected due to their prominence in the field of research and medical ethics as well as their particular relevance to the ethics of DCTs. These principles all serve as general guidelines for DCT designs, and they provide the necessary background for the following chapters, where these principles are further specified in the context of DCTs.

It is worth emphasising that these principles are not presented in any order of importance. As stated in the introduction, all of these principles will be treated as prima facie principles, which means that they can all be outweighed by competing considerations, and none of them will be treated as superior to the others. It is also worth emphasising that these principles do not belong to any particular moral theory or tradition. They are plausibly part of common sense morality and thus provide considerations that can be appreciated from a wide range of theoretical perspectives.

On this approach, these principles need to be weighed against each other when they come into conflict. When this happens, small costs in one area may be justified by large gains in another. For instance, a small risk of harm may be justified by the potential of large clinical benefits or huge gains in terms of autonomy. Other times a reasonable compromise must be found when different principles collide. Sometimes, however, as we will see in the following chapters, these principles also converge and give mutual support to particular considerations in relation to DCTs.

- **The principle of autonomy**: respect and support autonomous decisions.

Autonomy roughly means self-determination. Autonomous decisions are thus decisions made in accordance with one's own values, principles, and beliefs, and without undue influence, such as manipulation, coercion, and authority. To respect and support autonomous decisions therefore means 1) not to interfere with the decisions of others by unduly influencing their decision making, and 2) to provide positive grounds for reflection and understanding, e.g. by disclosing relevant information.

From this general principle, other principles or requirements in clinical research can be deduced, such as the requirement to tell the truth, to respect personal privacy, to disclose relevant information, to keep information confidential, and to ask for consent. As we shall see, even further specifications can be made in the context of DCTs.

- **The principle of beneficence**: promote the welfare of others.

Beneficence is about providing benefits to others. It is about making lives better by e.g. furthering health and abilities, satisfying individual preferences, and promoting positive mental states. Notably, this does not only include conferring benefits to others but also warding off any potential harms to their welfare. To act in accordance with the principle of beneficence thus means taking positive action to 1) provide benefits to others, 2) prevent harm from occurring, and 3) relieve existing harm.

Like the principle of autonomy, this principle forms the basis for many general requirements in clinical research, such as the requirement to ensure a positive balance of benefits vs. risks, to disclose beneficial health information, to minimise risks, to reduce potential pain, and to keep down burdens for participants.

- **The principle of non-maleficence**: do not cause needless harm.

Non-maleficence is about avoiding harm. Not just physical pain but anything that negatively affects the welfare interests of others. For instance, being needlessly disturbed by digital monitors during the night also counts as a harm. This principle is in some ways the mirror image of the principle of beneficence, which is about improving the welfare interests of others. In contrast with the principle of beneficence, however, the principle of non-maleficence does not require any positive actions, merely the abstention from causing unnecessary harm.

The principle of non-maleficence also grounds a number of general requirements in clinical research, such as the requirement not to select needlessly vulnerable participants, not to expose participants to unreasonable risks, and not to enrol more participants than necessary.

- **The principle of justice**: give people their due.

Justice is (amongst other things) about treating people fairly. It is about making sure that no one is systematically disadvantaged, discriminated against, or taken advantage of by others. Giving people their due in the context of clinical research thus means 1) not sacrificing individual rights on the altar of the common good, 2) promoting and respecting equal rights, and 3) distributing fairly the benefits and harms flowing from clinical research between researchers, participants, and the public.

From this principle follows a number of other requirements in clinical research, such as the requirement to select research populations fairly, to compensate participants for incurred expenses, to promote equal access to research participation, and to secure an appropriately diverse research population.

- **The principle of trust:** respect and promote trust.

Trust is about meeting expectations. It is about protecting personal as well as professional integrity, and it is about ensuring accountability. To promote trust is therefore a matter of 1) having fair and open arrangements, 2) adhering to moral and professional standards, and 3) taking responsibility when things go wrong. In many ways, trust is the glue that makes social operations possible. This is perhaps especially the case with research activities. If people did not trust the practice of research, it would be extremely difficult to enrol participants in clinical trials. It is therefore imperative that researchers maintain the trust of participants as well as actively foster good relationships between researchers and participants.

Like the other basic principles, the principle of trust similarly underlies a range of requirements and recommendations in clinical research, such as the requirement to provide honest information, to keep promises to participants, to make trial information publicly available, and to engage patient groups in study design.

Study design

Good study design is not only a matter of science but also a matter of ethics. Bad study designs waste scarce research resources and needlessly burden or even harm research participants. This also goes for DCTs. Study design is therefore an obvious place to start when thinking about research ethics in decentralised settings.

Generally, DCTs can draw on a variety of different decentralised elements, such as remote visits, electronic consent forms, asymmetric information disclosure, telecommunication, and satellite sites. They can also use these decentralised elements to a larger or smaller degree, ranging from fully decentralised designs to only partly decentralised study designs (hybrid trials). No matter which elements and to what extent they are used, however, decentralised study designs should ensure not only scientific validity but also ethical acceptability.

Recommendations

- **DCTs should promote beneficence and non-maleficence through selective inclusion of decentralised elements.** There are arguably many benefits to decentralised elements in clinical trials, as laid out in the Preface and Background of this guidance document. However, decentralised trial elements can potentially also negatively affect trust between researchers and participants by lessening personal interaction. Moreover, not all clinical trials are equally suited to use all decentralised elements in their study designs. For instance, trials involving medications with a high risk of serious side effects are not good candidates for a fully decentralised design. When incorporating decentralised elements into study designs, investigators should therefore provide reasons why these specific elements are well suited for a particular study. For instance, will the respective decentralised elements plausibly improve the welfare of participants? Will such elements promote autonomy? Will they promote justice in terms of distributing benefits and burdens more fairly? Do they further the moral rights of participants? Similarly, investigators should also be able to argue convincingly in the face of strong *prima facie* reasons against using specific decentralised elements in a particular study. That is, when introducing such elements can potentially have a negative effect on the values and rights expressed in the aforementioned basic ethical principles.

- **DCTs should promote justice by ensuring equal access to trial participation for people with different technical skills and electronic devices.** Study applications and online portals should be designed around user friendliness and they should be supportive of potential participants lacking advanced technical skills, e.g. in terms of navigating applications, creating user profiles, and managing settings. Moreover, studies should not be designed solely for particular electronic devices (e.g. iPhones or Apple Watches), unless researchers can supply all potential participants with such devices and participation does not require intimate knowledge of the specific device.

- **DCTs should promote autonomy by incorporating participant preferences into the study design.** Research participants may have different preferences in terms of their participation. One size rarely fits all. It is therefore important that decentralised elements are utilised in accordance with participant preferences, and that non-decentralised alternatives are offered to a reasonable extent where applicable. For instance, participants should ideally be able to pick their own time slots for study activities and take part in planning their participation. Face-to-face meetings should be offered to participants who feel the need to discuss information in person, and video calls should be offered to participants who prefer to communicate with staff from a distance.

Recruiting online

Just like other parts of research, recruitment of trial participants is starting to move away from traditional research sites. More and more frequently, participants are recruited online through social media, digital registries, and online portals. This raises both new opportunities in terms of enrolment and diversity in clinical trials as well as new challenges. On the one hand, some of these challenges are analogous to traditional ethical challenges in relation to recruitment. For instance, just like it could be considered offensive to recruit participants for a study on HIV drugs outside nightclubs for gay men, it could similarly be considered offensive to do so through online LGBTQ+ groups. On the other hand, some ethical challenges related to online recruitment are rather novel, such as navigating through issues of privacy in relation to social media recruitment.

On a general level, recruitment can be both active and passive. In active recruitment, contact is initiated by the recruiter, and potential participants are confronted with making a choice (including not replying). A typical example of this would be a doctor informing eligible patients about a relevant study. In passive recruitment, however, contact is initiated by potential participants through their own volition. A typical example of this would be a potential participant contacting a researcher after seeing a flyer in a doctor's waiting room (or a post on a social media page). Generally, passive recruitment is preferable to active recruitment in terms of respecting autonomy, as passive recruitment is generally less intrusive, but it is worth noting that neither are inherently morally wrong and that both active and passive recruitment can be overly aggressive or offensive depending on the context.

Recommendations

- **DCTs recruiting participants through social media should use privacy enhanced messaging.** Virtually anything that can be clicked on through social media is used for data collection, which is further used for advertisements and development purposes. This is all part of the usual terms and conditions that users agree to when signing up. In the context of research, however, we usually require further protections for participants in addition to requiring their consent. For instance, procedures must be in place to minimise potential harm and protect the privacy of participants in a clinical trial. When designing online recruitment material, it is therefore important to consider how phrasing can be used to minimise the risk of potential participants needlessly exposing themselves. For instance, instead of referring specifically to patients with certain diseases, refer to the general topics of the study. This

not only protects participants against future privacy violations but also lessens risks of growing distrust when participants suddenly begin to receive new advertisements implying knowledge about personal disease history or health.

- **DCTs recruiting participants through social media should be mindful about following relevant social media guidelines and be able to justify any transgressions**. Social media sites (and groups) come with terms and conditions that may have relevance in terms of recruiting participants for clinical research. When recruiting through social media, it is therefore important to know any potential conflicts with official guidelines and to provide reasons for any transgressions. For instance, if certain rules are not followed in practice they may be considered solely pro forma. Similarly, many groups on social media have specific rules for membership and posting. Before joining any particular group or posting in any particular online space, it is therefore important to seek out relevant permissions and knowledge about appropriate guidelines.

- **DCTs recruiting participants through social media should respect privacy by closely moderating or disabling any commenting features on recruitment posts.** It is easy to forget that online comments are visible to others, and many people are used to communicating through comment sections on social media. In the context of clinical research, however, this may not always be appropriate in terms of personal privacy as it can lead to needless self-exposure for participants. Moreover, this could potentially jeopardise study results if participants disclose information to researchers or each other in the comment section that can influence the results or interpretations of the study. It is therefore important that comment sections are closely moderated (e.g. with pending permissions) or in some cases even disabled from recruitment posts.

- **DCTs should be mindful about choosing the right social media platforms.** Different social media platforms have different demographics, which should influence choice of platform for a particular research project. For instance, Instagram has more female users than Facebook, and SnapChat has younger users than LinkedIn. They also offer different opportunities in terms of recruitment, e.g. different visibilities and permissions for user generated groups. Beyond meeting enrolment

demands, however, researchers should also consider how recruiting participants through different social media platforms impacts diversity in terms of their research population.

- **DCTs recruiting participants through social media should be careful about growing distrust by advertising directly to individuals.** Social media allows for advertisements directly aimed at specific groups of people satisfying certain criteria. This is why it can be a powerful tool for research recruitment. However, this feature can also have a chilling effect on people when they learn that the social media in question knows particular facts about them, especially when these facts are related to their health. Although this does not necessarily violate their privacy, recipients may still be uncomfortable with the impression that researchers are using their personal information to target them for study participation. Naturally, this concern is directly proportionate with how sensitive or private people consider the relevant information, which should be considered closely when advertising directly to individuals.

- **DCTs using online portals or digital registries for recruitment purposes should respect autonomy by periodically asking registered individuals for re-consent.** Many companies and institutions are offering interested individuals to register for contact concerning relevant future research projects. Besides the benefits in terms of enrolment, there are also many advantages to this constellation in terms of autonomy. Interested individuals can communicate in advance that they are open for contact, and fewer uninterested individuals will thus be bothered with recruitment attempts. As digital registries are easy to maintain and uphold, however, individuals in the registry may lose interest in being contacted over time, which should be respected not just in terms of providing easy opportunity to be removed from the registry but also in terms of getting registered individuals to re-consent.

Informed consent

Informed consent is a cornerstone in research ethics and it is the golden standard for consent in the context of clinical research. It requires a voluntary and appropriately informed decision by a competent individual and it is therefore closely connected to the principle of autonomy. However, the consent requirement is not only grounded in respect for autonomy but also in the principle of beneficence, as it protects potential participants by giving them information about potential harms. Moreover, it promotes trust by increasing transparency concerning study procedures, risks, and potential benefits.

Generally, information disclosure in decentralised settings can take on the form of synchronic or non-synchronic disclosure. In synchronic disclosure, participants and researchers are present at the same time, e.g. during a video or telephone call. This allows both parties to ask questions and get feedback directly in real time. In non-synchronic disclosure, however, information is given without the presence of both parties at the same time. This allows participants to take in the relevant information when they want to and to watch or listen to study material multiple times. As such, both models have strengths and weaknesses in terms of informed consent but it is worth emphasising that these models are not mutually exhaustive and elements of both may supplement each other in a particular research project.

Recommendations

- **DCTs should respect personal autonomy and promote justice by supporting participant understanding through technological means.** Many studies indicate that research participants often fail to understand central terms in the context of clinical research, such as randomisation or even the concept of research itself. This is of course problematic from the point of *informed* consent. When possible, decentralised elements should therefore be used to promote understanding through technological means such as multimodal information material (visual, auditory, reading) that appeals to different kind of learners. For instance, researchers can use oral information in combination with videos to present complex material. Mouse over functions can be used to provide general definitions and word explanations in electronic reading materials. Expandable text boxes can be used to explain central terms. Importantly, such features are not a replacement for jargon free and accessible information to participants but rather meant to support disclosure of clear and concise information. This is not only important in terms of informed consent but also in terms of securing equal access to participation in clinical trials.

- **DCTs should promote personal autonomy and trust by increasing transparency of data collection, data usage, and data flow through studies.** In modern trials, health data often moves through several different parties, which can make it difficult to understand how data travels and where it ends up in a particular study. It is therefore important to convey this information to potential participants in an accessible format, such as a geographical data map using arrows to show how data flows through different sites and partners involved in the study. Such information may not only be valuable in terms of informed consent but may also promote trust that researchers will treat the data collected in the study responsibly.

- **DCTs should respect personal autonomy by inviting participants to reflect on their decision to take part in the study.** Informed consent is a process. It is not just a signature on a form. While not particular to DCTs, less interaction between researchers and participants means fewer chances for shared reflection, and therefore calls for increased focus on the informed consent process throughout the study. Research projects using study applications can use periodical notifications (with permission from users) that probe participant satisfaction with the study and reminding dissatisfied participants that they can withdraw from the study without giving any reason and with no further consequences. Staff interacting with participants from a distance should similarly make a point to discuss continued participation in the study.

- **DCTs should respect autonomy and protect participants from harm by ensuring that they have understood the relevant information.** The requirement for informed consent in clinical research do not merely involve non-interference and providing information but also probing participants for understanding. This usually happens during synchronic information disclosures. For projects without synchronic information disclosure in the consent process, this means that proper comprehension must be ensured through other means. For instance, digital quizzes can be utilised to ensure that potential participants cannot sign the informed consent form without having read, watched, and understood the participant information. Time spent reading the material or viewing video information can also be tracked and used to gauge participant understanding, with the permission of users. Buttons can also be used strategically to engage participants with study material.

- **DCTs should respect autonomy by avoiding excessive use of medical terms and symbols in information material (videos, graphics, written)**. Many studies indicate that research participants often mistake the purpose of clinical research (to produce knowledge) with the purpose of health care (to care for patients), potentially leading participants to overestimate the potential benefits and/or underestimate risks of research participation. This confusion is often referred to as the therapeutic misconception, which is considered a challenge in terms of informed consent as it impedes understanding. Moreover, excessive use of medical terms and symbols may also unduly influence participants through misplaced authority, raising additional concerns in terms of respect for autonomy. Importantly, this misconception is not only concerning in terms of consent, which requires information and understanding, but also in terms of harm when participants underestimate risks. This is especially concerning in cases where researchers have underestimated risks as well. It is therefore important that participants are not needlessly confused or influenced by terms and symbols from the world of health care. For instance, do not refer to participants as patients. While the respective individuals may be patients in other settings, they are participants in the context of clinical research. Also, avoid unnecessary clinical markers such as stethoscopes and doctor robes that may needlessly add to the therapeutic misconception.

- **DCTs using video or other graphic information material should promote justice by painting an inclusive picture of potential trial participants and research staff.** The research population in many clinical trials is relatively homogeneous, lacking clear similarity to the population suffering from the disease, e.g. with a disproportionate number of people older than 65 years or members of various minority groups, owing to strict inclusion criteria used to reduce variability in the results. This means that some adverse effects are potentially not caught during studies and that results on proper dosages may be skewed against certain parts of the population, which can lead to systematic disadvantages. If DCTs are to fulfil their potential for diversifying research populations, it is important that they appeal to a broad segment of the population. For instance, researchers should choose inclusive images from stock photo suppliers or members of the research team, and avoid unnecessary cultural or religious symbols that may in effect exclude certain members of the population.

- **DCTs using video material should be mindful about keeping the material relatively short.** Although video material are in many ways better suited to grab attention than dialogue, there are limits to how much information people can process at a time. Especially when the subject material is cognitively demanding. As a rule of thumb, research video material should not last longer than 15 minutes, which is around the general attention span for e-learning videos. Videos exceeding more than a couple of minutes should either be broken into smaller parts or have a table of contents with time stamp links, ensuring easy access to different parts of the video and adding to the replay value of the material.

- **DCTs should respect autonomy and promote trust by ensuring proper technical training in telecommunication for researchers conducting video calls with participants, as well as ensuring plans for technical assistance when needed.** Telecommunication has many potential advantages for research participants, as it allows them to communicate with researchers from a distance. Despite recent advances in telecommunication technology, however, technical difficulties may still arise during calls, which can lead to complete breakdowns in communication. Loss of internet connections, crashing applications, and poorly sounding microphones are also part of life in decentralised settings. It is therefore important that researchers are adequately trained and prepared to handle any technical difficulties, and that appropriate plans for technical assistance or alternative modes of communication are in place, in order to ensure sufficient understanding for participants and to instil trust in researchers.

On the app

The use of study specific applications is becoming more and more frequent in the scientific community, offering ease of data collection and information disclosure. Such applications can be used to disclose information, collect data, schedule appointments, as well as facilitate communication between researchers and participants. In combination with sensors and monitors, such applications can collect large amounts of data in short time with huge potentials for clinical research.

In general, study applications can collect data actively or passively, depending on whether data is collected through direct user input (active data collection) or without any direct input from users (passive data collection). A typical example of the first kind would be participants actively registering information in the app, whereas an example of the second kind would be continuous monitoring of participants with a wearable device. Both have strengths and weaknesses in terms of ease of use, reliability, and participant control.

Recommendations

- **DCTs should promote autonomy and trust by ensuring privacy by design when it comes to study applications and online portals.** Most users of electronic systems use the default settings of the respective system, due to lack of technical skills, unawareness, laziness, or simply lack of interest. However, where privacy is concerned, users often fail to realise the potential negative consequences of having their data tracked and collected. Moreover, disregarding privacy can lead to distrust between participants and researchers in retrospect, if participants later on become uncomfortable with the use of their data. It is therefore important that privacy considerations and settings are built into all relevant study systems and that they are turned on by default. Study applications should not start tracking data without consent, and they should be transparent when it comes to data collection, especially if this happens outside of using the application, where users are less aware of data tracking.

- **DCTs should respect personal autonomy by giving participants easy access to withdraw from studies**. Study applications and online portals should avoid the dread of terminating online services. Options to withdraw from studies or online portals should be immediately visible from the settings menu. Importantly, while final confirmation may be sought out, participants should not be required

to complete a questionnaire or give any particular reason if they want to withdraw from a particular study.

- **DCTs should respect personal autonomy and promote beneficence by minimising app notifications.** Modern technology is full of potentially distracting features, competing to attract user attention with potential detrimental effects on both our welfare and personal autonomy. These effects are not owed to any device or application in particular, but to the fact that all these digital disturbances have a powerful cocktail effect on our attention. This also goes for study applications, not least concerning applications using notifications to attract attention from users. While such notifications may have a legitimate role to play in a study application, it is recommended to keep study notifications to a minimum unless specifically chosen by participants.

- **DCT should promote privacy by educating the participant on how to remove the app from a personal electronic device.** The only reason for installing a study application for DCTs is to enable participation in a given trial. When the trial is finished, this reason disappears and it is therefore important to make the participant aware that the app should be deleted and provide detailed instructions for how to do so. By following these instructions, the participant should feel confident that no data files related to the study application or logging of interactions with other apps are still present on the device. This will ensure the privacy of the participant and trust towards the DCT study application provider and sponsor.

At home

One of the key benefits of DCTs is that participants are able to participate from the comfort of their own home. For people with disabilities or care taking obligations, this can be hugely important in terms of securing equal access to trial participation. As will be laid out in the following, however, certain considerations also warrant attention and different values need to be balanced when clinical trials move into people's houses and homes.

Home is where the heart is – not (at least not usually) where the heart monitor is. This may soon change, however, and it is worth considering how this change will affect individuals, homes, and families. The medical sphere has expanded throughout the last thirty years reaching into more and more intimate parts of our lives. The comfort of our own homes is perhaps one of the last bastions against this development, which should be kept in mind when using participant homes as trials sites.

Recommendations

- **DCTs should balance the benefits of participating in trials at home with the potential harms of medicalising personal space.** Due to recent trends in telemedicine, homes are increasingly becoming sites for health care staff and hospital equipment. While this may have obvious advantages for patients, it may also negatively affect the impact of the home when it comes to personal welfare. This point also stands in relation to DCTs. Especially in relation to studies involving monitoring or visiting participants in their homes, potentially blurring the distinction between the private and the public domain. Researchers should therefore consider closely using the homes of participants as sites in clinical research in light of the possible alternatives, potential benefits, and participant preferences. In any event, researchers should take care not to needlessly interfere with daily routines and rituals, as well as the lives of family members, and to minimise any disturbances caused by trial participation.

- **DCTs should protect the privacy and confidentiality of research participants by ensuring continuity in research staff visiting or communicating remotely with participants.** Home visits and video calls have many potential benefits for research participants, especially for participants with disabilities or care taking obligations. This is particularly so in relation to trials with many scheduled visits. However,

it is worth remembering that letting other people into your home, through a video screen, or in person, can potentially also expose a lot of information about you. To the extent possible, home visits and video calls should therefore be performed by the same member of the research team each time. This not only protects participants and their family members against excessive exposure but also has the added benefit of building and increasing trust between participants and researchers.

- **DCTs should protect participants from potential harm by ensuring proper staff training in the practice of telemedicine.** Communicating through the phone or through a video call is different from communicating face to face. For one thing, researchers have to rely on only one or two senses when communicating with participants over a phone or video call, respectively. Such losses in nuances may not ordinarily cause concern but they may nevertheless be important when communicating about health. Especially when disclosing or receiving complex health information. It is therefore imperative that research staff communicating with participants are properly trained in the practice of medicine from a distance, as losing important details in a research setting may expose participants to risks of harm.

- **DCTs should protect participants from harm and ensure data quality by facilitating proper instructions to participants in terms of using devices or medications at home.** When trials go remote, participants typically take on more responsibilities in terms of treatment and diagnostics away from traditional research sites. While this may be convenient for both researchers and participants, proper care should be taken to ensure that participants are able to operate required equipment and comply with protocols from home. For instance, successful diagnostics through photo or video requires proper lighting and positioning of the camera, conditions which are often not optimal at home. A failure to navigate these conditions, however, may cause harm to participants and lead to poor data quality. It is therefore imperative that participants receive proper instructions on any study procedures that they need to follow, and that their ability to operate required equipment and follow protocol is properly evaluated in accordance with potential risk.

Post-trial

Ethical considerations in clinical trials do not only arise before and during a study but also after a trial has ended. Such considerations not only include obligations of care but in some cases also ethical issues concerning access to medication or medical equipment after a trial. For the present purposes, however, the most relevant considerations pertain to feedback from participants and disclosure of relevant study information, as participants in DCTs are, all else being equal, more likely to lose contact with researchers after a trial has ended.

Many different decentralised trial elements can be used to gather feedback from participants and to disclose relevant study information after a trial has ended. For instance, online surveys and various online portals can be utilised to collect data, study applications can deliver video material, and relevant information can be disclosed through sufficiently secure digital mail. Through such tools, DCTs can help to meet certain post-trial obligations.

Recommendations

- **DCTs should promote trust and beneficence by inviting feedback from participants.** The use of decentralised elements in clinical research is still in an early phase, and will remain a new experience for many research participants in the coming years. It is therefore important that feedback on decentralised elements is gathered during and after the clinical trial to improve the experience of participants and foster trust between researchers and participants. For reasons of beneficence and trust, feedback should include not only issues pertaining to efficacy in terms of treatments but also the subjective experience of participants concerning different decentralised elements. As mentioned earlier, trust is paramount to decisions about research participation and trust is at least partly a matter of meeting reasonable expectations. It is therefore important to know when decentralised elements fail to do so.

- **DCTs should provide easy opportunities for participants to know when studies end.** Many participants in clinical trials suffer from chronic conditions and wish to participate in multiple trials over the course of their life with the disease. However, for long-term follow-up in trials, it can be difficult to keep up with end dates of visits far out in the future. Knowing when studies end is

therefore not only key for participants in terms of getting feedback from researchers, but may also be important knowledge in relation to taking part in new research projects. Moreover, the ending of a trial also prompts reflection and feedback from participants, which can potentially get lost when end dates are unclear.

- **DCTs should promote beneficence and autonomy by disclosing study results to participants in accordance with their preferences.** One of the main benefits for participant in clinical research is carefully disclosed information about their own health as well as individual study results. Study applications and online portals can be used to provide feedback to participants, and video materials can be used to debrief participants and inform them about the overall results of the study. Sensitive health information or health information with diagnostic value, however, should always be disclosed synchronically by a trained professional subjected to professional standards and rules of confidentiality. When disclosed appropriately, such information not only confers benefits but also promotes trust by treating participants as ends in themselves and not as subjects solely being used for the ends of others. Importantly, however, the principle of beneficence does not only provide participants with a right to know relevant health information but also a right not to receive such information.

Concluding remarks

The practice of scientific research is inherently innovative. Most often for the better, but sometimes also for the worse. Our history is full of examples of both, often driven by technological advances just like the developments we currently see in the field of DCTs.

In order to promote beneficence and maintain trust between research participants, researchers, and society, however, it is imperative that this development is steered for the better. Especially considering the rapid nature of technological advances, providing more and more possibilities for decentralisation in clinical trials. Reaping the benefits of these possibilities while minimising the costs and balancing the relevant concerns will require ongoing discussion and critical reflection.

In this regard, particular attention should arguably be paid to protecting the rights and interests of research participants. They often carry a heavy burden in clinical research, sometimes with little to no chance of direct clinical benefits. Decentralised elements should take away from this burden without introducing other significant concerns in the process.

Moreover, special concern should be given to the informed consent process. As previously mentioned, consent is not just a signature on a form, but rather the ongoing process of taking part in a research project throughout every part of the study. Decentralised elements should therefore not just be used to support understanding, reflection, and decision-making at the beginning of a trial but throughout all stages of a research project.

In the coming years, possibilities for decentralisation will presumably expand and widen in clinical research, not least due to further developments in telemedicine. Navigating through this landscape will require guiding principles and ethical reflection. With this document, we hope to have provided some landmarks, as well as a framework for fruitful discussion, ethically sound innovation, and solid participant protection in the context of DCTs.

Further readings

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