ABOUTOpen
Clinical research

AboutOpen | 2023; 10: 22-26
ISSN 2465-2628 | DOI: 10.33393/ao.2023.2546

POINT OF VIEW

Open Access

Decentralized Clinical Trials in Italy: state of the art and future perspectives

Elisa Zagarrì, Stefania Frasson, Antonella Valerio, Gualberto Gussoni

FADOI Study Center, Milano - Italy

ABSTRACT

Clinical trials are an essential source of high-quality evidence for the assessment of efficacy and safety of healthcare interventions. Nowadays the main criticality of the traditional clinical trial model is perhaps the need to improve patient selection and management, in terms of initial identification, recruitment and retention.
Digital technology offers operational solutions that can facilitate many of the activities involved in clinical investigation. Decentralized Clinical Trials (DCTs) could be a new option that provides for the use of remote instruments/methods/activities in the different stages of a clinical trial, so that a range of procedures (such as informed consent, medical visits, administration of a drug or use of a medical device, measurement of clinical parameters, diagnostic testing etc.) can be moved from the research hospital to the patient's home.
Also in Italy the interest in DCTs is progressively growing, and thanks to their potential benefits DCTs can lead to significant advantages not only for patients, but also for the National Health Service and for the country as a whole. It is important that this interest should act as a stimulus, prompting timely initiatives in order to promote and regulate this new methodology for conduct of clinical trials to avoid the risk that, while other countries will be actively involved in the promotion and leading of DCTs, Italy will be selected only as "control arm".

Keywords: DCT, Decentralized Clinical Trial, Remote monitoring , e-consent, digital health

Introduction

Clinical trials are an essential source of high-quality evidence to demonstrate the efficacy and safety of healthcare interventions. Traditional trials, with procedures largely carried out in a hospital setting, have the advantage of taking place in a controlled environment. Despite this, their format is under increasing pressure in relation to efficient use of resources, cost containment and, if possible, compression of the overall time frame for a trial's completion. But the main criticality of the traditional clinical trial model is probably the need to improve patient management, in terms of initial identification, recruitment and retention. The need to identify appropriate formulae for decentralizing clinical trials and enabling their implementation outside hospital facilities became an urgent priority at the height of the CoViD-19 pandemic: if the regulatory authorities had not waived certain procedural requirements at that time, and technology had not enabled efficient application of various innovative practices to expedite data collection and related quality control measures, large numbers of clinical studies would have had to be curtailed or would never even had started (1).

Digital technology now offers operational solutions that can facilitate and move from hospital to patient's home many of the activities involved in clinical investigation: this enables trial implementation models offering the combined advantages of quality, greater flexibility in the related procedures and easier, more widespread access for patients.

DCT: definition, history and comparison to traditional study models

A number of definitions of (remote) decentralized clinical trials (DCTs) are available, one of the most known being proposed in the context of the Trials@home project (a joint initiative by the European Commission, the Innovative Health Initiative – IHI and the European Federation of Pharmaceutical Industries and Associations – EFPIA).

According to this definition, DCTs are *"… clinical trials that make use of digital innovations and other related methods to make them more accessible to patients. By moving clinical trial activities to the participant's home or to other local settings, this minimises or eliminates physical visits to a clinical trial centre"* (2).

In other words, DCTs should be seen as an option to run a clinical trial that provides for the use of remote instruments/

Received: Decembe 12, 2022
Accepted: January 23, 2023
Published online: February 10, 2023

Corresponding author:
Elisa Zagarrì
Fondazione FADOI – Centro Studi
Piazzale Luigi Cadorna 15
20123 Milan - (Italy)
mailto:elisa.zagarri@fadoi.org

methods/activities that can change modality and/or site of execution of a number of procedures (such as informed consent, medical visits, distribution and administration of a drug or use of a medical device, measurement of clinical parameters, diagnostic testing). The choice of which instruments/methods/activities to implement in the study is determined by the specific needs of the target population, the nature of the research question, the types of clinical assessment to be carried out, the type of therapy under study, and the phase of development concerned. Theoretically, DCT can be fully remote, but more frequently they are hybrid, combining procedures performed in a decentralized and in a traditional way.

DCTs are not an absolute novelty. The first entirely web-based clinical trial dates back to 2011 (3). It is difficult to collect precise quantitative data regarding the numbers of completed or ongoing DCTs, but the forecasts point to an exponential increase of these studies in the next few years [Frontiers Health21, Milano, Session DCT. Research2Guidance 2021]. With specific reference to Italy, a recent survey of 25 companies belonging to the National Association of Pharmaceutical Companies/Farmindustria examined data for the period 2019–2021: 60% of trials promoted by respondents in that time frame included at least one digital or remote component (4).

Recently, the global Contract Research Organization IQVIA published an analysis of a dozen of DCTs to determine how this approach compares to traditional study models. The data shows that the DCTs delivered time and cost efficiencies at virtually every point in the clinical research journey: the benefits included an average of 78% reduction in recruiting time (related to opening participation to a broader patient population), and 15% reduction in dropout rates (likely due to the decreased time and travel burden experienced by participating patients and their families/caregivers, and increased engagement of patients by means of electronic reminders) (5). Although each study considered in this analysis saw different results based on the type of trial, size, location, and which decentralized elements were included, they all experienced benefits that delivered time and cost savings.

Interest in DCTs is progressively and globally growing. In Italy, in 2022 and with a view to efficient and timely implementation of DTCs in the Country, two White Books were published on this topic, one promoted by the Istituto Superiore di Sanità/ISS in collaboration with Farmindustria (4), and the other by Fondazione Smith Kline and the Italian Scientific Society of Internal Medicine FADOI (1).

The European regulatory framework

The technologies and activities/procedures that can be used in decentralized mode must guarantee the same levels of patient safety and personal data protection as traditional clinical trials. This creates challenges that are far from trivial in a regulatory perspective. In this respect, the scenario continues to evolve rapidly, but at the time of writing a specific regulatory framework for DCTs remains an unfulfilled need, both in Italy and at international level. The legal and procedural requirements for DCTs must therefore still be sought in sources that are broader in scope, like Regulation (EU) 536/2014 for clinical trials, Regulation (EU) 679/2016 (GDPR) for personal data protection, Regulation (EU) 745/2017 for medical devices, ISO standards (13485/2016 and 14155/2020, in particular) and the ICH GCP E6 (R2) Guidelines (currently undergoing revision, to include *inter alia* preparation of a specific annex on non-traditional interventional clinical trials).

At the same time, however, there is no shortage of documentary sources and projects devised to establish overall guidance and an appropriate regulatory framework for "modernization of clinical trials". In the European Union, the European Medicines Agency (EMA), in collaboration with the European Commission and member states'national medicines agencies, recently introduced an initiative called "Accelerating Clinical Trials in the EU" (ACT EU), to update modalities for the design, launch and implementation of clinical trials (6). In the context of this initiative, European recommendations for DCTs are expected to be issued by the end of 2022. The EMA is also in the process of drafting recommendations regarding the use and validation of computerized electronic data collection systems for clinical trials. In individual countries within Europe, the national regulatory agencies of Sweden, Denmark and Switzerland have launched awareness-raising initiatives, or issued guidelines specifically dedicated to DCTs (7-9). The CoViD-19 emergency prompted regulatory authorities to adopt timely measures enabling some experimental activities in digital, decentralized mode. In the European Union, of note is the "Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) Pandemic" (10). Though the guidance is made up of temporary recommendations for the pandemic, these indications are key elements also with a view to the future, and for the implementation of DCTs as well. Looking at the specific case of Italy, AIFA responded to the pandemic by authorizing: (i) collection of the patient's informed consent by means of validated electronic tools; (ii) direct-to-patient delivery of the investigational drug (preferably via the hospital pharmacy); (iii) at-home implementation of procedures specified in the study protocol, to be carried out by trial facility staff or contractors, under the supervision of the principal investigator (e.g., clinical evaluations or administration of complex therapies); (iv) completion of biochemical and/or instrumental analyses/examinations in facilities close to the patient's home; (v) possibility of remote source data verification (11). The time has now come to understand whether, to what extent, and subject to what specific conditions these temporary derogations granted during the pandemic will continue to be routinely adopted.

Potential benefits and critical issues of DCT implementation

The interest of research stakeholders for DCTs is linked to a series of potential advantages that this study model entails, but it is understandable that an effective implementation of DCTs must also take into account their possible limitations. Table 1 shows and indicative and non-exhaustive list of potential benefits as well as of doubts/limitations/needs for DCTs (1).

The DCT, incorporating as it does many new technical and logistic features, entails the need for careful thought about proper assignment of roles and responsibilities among the

TABLE I - Main advantages and uncertainties related to the implementation of DCT (modified from Gussoni G. – Editor (1))

Potential benefits	Doubts/Limitations/Needs
DCTs offer a new type of studies, with advantages in terms of procedural simplicity and flexibility	This type of study can be difficult to implement for certain treatments and diseases particularly complex to manage
Greater ease of access for patients (e.g. having little or no travel to a trial facility), enhancing representativeness/generalizability of results	Some patients may not be fully available to participate in DCTs (e.g. elderly and/or with nobody to help them, with limited digital skills etc.)
Higher patient retention rates and better compliance (thanks to home setting, use of electronic reminders etc.)	Further experience is needed to provide evidence regarding the real capacity of DTCs to enhance patient enrollment/retention
Electronic informed consent gives more time to review the information on the study, and possibly with support material (infographics, video)	Some patients may feel more reassured by personal contact with their attending physician
Evaluating endpoints less readily examinable in a traditional trial (e.g. 24/7 monitoring of clinical parameters), and in a real-life setting (particularly for patient related outcomes)	In the analyses of results, must be paid to the case in which, in the same and possibly in the same patient, measurements are made in different contexts (e.g blood pressure self-measured by the patient at home, or measured by the doctor in hospital)
To collect data non stop could enhance detection of rare events and timely identification of adverse events	Timely management of adverse events/alerts (feasibility/legal aspects)
Wearable devices enable real-life and real-time recording of biological parameters	Wearable devices may be in some cases inconvenient or uncomfortable to wear. If visible, they could entail a breach of confidentiality regarding patient's participation in a trial
Remote and automated data collection can favour quality and traceability	Remote data collection is subject to criticalities, taking place in a less "protected" setting than a research facility
Technologies are available to be applied to each stage of a clinical trial, and their performance are progressively growing	Health technology entails an increased need for security measures against possible breaches of data security during collection, transmission and/or storage
The use of local laboratories and diagnostic facilities reduces patient travels and the commitment of hospital centers, and promotes the quality of local diagnostic laboratories	In cases where the DCT involves use of local clinical laboratories and diagnostic facilities, the sponsor and/or investigator will be faced with the process of standardizing results
Overall costs for management of the project for sponsors tend to be lower, as does the cost per single data item (given the considerable mass of data generally involved in DCTs)	Studies focusing on the economic impact of implementing DCTs are still limited. Sponsor will probably have to factor in higher costs related to supply/management of technological support and remote oversight. Research facilities have to invest in training, know-how and acquisition of the necessary technologies
DCTs have the potential to generate positive fallout for investigators/clinicians and for the hospital organization as a whole: rationalizing the need for on-site control, shortening times for collection and recording of data, for drug management (with the implementation of direct-to-patient delivery), and probably for monitoring and auditing	The potential benefits have to be weighted up against the need to manage interaction with other actors (e.g. digital service provider, and/or those dispensing services at the patient's home)
The health service can benefit from greater involvement of outlying and territorial hospitals in clinical research, as well as of multidisciplinary and multi-professional groups (doctors, nurses, psychologists etc.)	It remains to be seen how far DCTs can really be integrated into the clinical activity of the investigator and the research team, without significant increase in expense other than for initial outlay

actors concerned. Indeed, and as an example, it is quite possible that third parties will manage sample collection, administration of questionnaires, dispensation of the investigational drug and performing of study procedures at the patient's home or elsewhere. This raises the need for guidelines specifying the parameters for proper selection of the providers concerned, as well as the training they will be required to complete; further, the responsibilities and roles (responsibility – execution – supervision) of Investigators/Sponsor/Provider of services are to be defined and regulated, within the terms of contracts/agreements among the parties and complying with the spirit of the current Good Clinical Practice (GCP) version.

Given the nature (and the often considerable volume) of the data collected, in DCTs it becomes even more relevant than in traditional clinical trials to examine the legal question of whether secondary processing of the data collected can be envisaged, for purposes not strictly connected to the trial itself. This is a complex subject that would need to be analyzed more extensively and in depth, and could lend itself

to a variety of interpretations, reflecting different regulatory sources (Regulation (EU) 536/2014, the GDPR; the Italian Code of Personal Data Protection; a national law of 2021, issued as Decreto Legislativo 139/2021). These regulations, obviously subject to conditions of proportionality and to appropriate safeguards for the patient's rights, seem on the whole to leave room for possible authorization of data processing outside the scope of the study protocol. This possibility can apply "for reasons of major public interest (for example, in relation to health)", but also "to promote the quality and safety of healthcare". The patient concerned must in any case be made aware, in the information sheet provided, of all the purposes for which the data will be processed: if this was not done at the outset, consideration can be given to providing the information concerned within a reasonable period of time thereafter (Article 14 of the GDPR).

DCTs require specific know-how and skills, so as to enable correct management of the technologies used, the masses of data collected and the remote interaction with the patient. Decentralization of research and the use of digital technologies are conducive to even greater patient engagement in the trial, making them to all intents and purposes largely responsible for data collection. In this respect, patients' levels of health/technical literacy must be given due consideration, providing specific training where necessary so as to ensure that any initial shortcomings in these areas do not become an obstacle to enrolment and to proper running of the study. More generally, current developments in clinical research as a whole – and DCTs in particular – underline the importance of creating new job profiles for the management of clinical trials and of the data they generate (e.g., data scientists, bioinformaticians), while also updating the skills required for existing job profiles (e.g., monitors and data managers/clinical trial coordinators). The knowledge and competencies required extend not only to technology, but also to communication skills.

In addition to technical, legal, regulatory matters, there are also ethical questions that must be taken into account when planning and running DCTs (12). From an ethical viewpoint, decentralization brings potential benefits for the patient – in terms of justice (understood as eligibility to access trials and innovative therapies), autonomy and beneficence/beneficiality; at the same time, there are also risks. Among the major criticalities, it is important to take into account relational implications. A patient receiving treatment at home will have less opportunity to interact with other trial participants who have the same clinical condition in common, thus ruling out the possibility of comparing notes in terms of effects, consequences and expectations generated by trial participation. Equally important is the need to ensure that a DCT makes provision for communication as close as possible to the dynamics of a face-to-face visit, thus enabling the patient to feel properly supported and cared for. In other words, the quality of the doctor-patient relationship must not be undermined, an important consideration in this regard being the need to maintain constructive empowerment of the patient. To this end, the physical distance separating the patient from the trial facility must be put into a reassuring perspective by fostering healthcare staff's skills in managing this type of communication, and by making the technology involved as user-friendly as possible.

Conclusions

The logic of clinical trials should be to address patients' needs, improve the capacity of generating knowledge that can be applied to clinical practice, and guarantee the quality of the evidence produced. DCTs reflect a process of evolution and should be seen as an option that takes its place alongside the traditional model, with no loss or diminishment of the study's value and no change to the recognized methodological standards required for the generation of evidence.

Currently, the national and/or EU legislative framework is limited to on-site clinical trials in hospitals, while no specific provision is made for DCTs. This lack of a dedicated regulatory framework is expected to be filled shortly, but the potential heterogeneity of procedures in DCTs is plausibly very high and hard to comprehensively addressed. In a situation of relative uncertainty, to prevent rejection of applications and/or adjournment of the required assessments, it is recommended that study protocols and related submissions to regulatory authorities and Ethics Committees should fully describe the study's operational features, with specific reference to the main activities scheduled in decentralized mode.

Thanks to their potential benefits, along with a more general contribution to the furtherment and modernization of clinical research, DCTs can hold out significant advantages not only for patients, but also for the National Health Service and for the country as a whole: decentralization of clinical research can certainly bring positive fallout for health and welfare, for the medical and scientific culture of the population at large, for the economy and for employment. The success of DCTs could depend on a number of factors

- if these studies will be financially sustainable by healthcare and industrial systems
- if the regulatory framework will be rigorous but not penalizing
- if DCTs will be become integrated into the broader dynamics of research, and more generally of medical care as a whole, without creating additional burdens for healthcare professionals and health systems
- if a true "democracy of digitization" will be achieved
- if we will be able to promote digital literacy between citizens and healthcare professionals
- if a balance is found for the patients that does not penalize the "social" and "relational" dimension of the disease and course of treatment.

Evidence in this regard is still limited, in Italy as elsewhere. However, there is a greater likelihood of achieving the level of integration envisaged if not only the health system, but the country in its entirety, commits to the task. The implementation of DCTs is not limited to the mere adoption of technological solutions, but requires a paradigm shift in health management, moving to a patient-centred model of clinical trial activities. It will be important to ascertain whether the envisaged transformation of Italian healthcare in the next few years, with the National Recovery and Resilience Plan/Piano Nazionale di Ripresa e Resilienza (PNRR) as a major driver, will also bring advantages in terms of the enabling conditions for DCTs. A further precondition is that the National Health

System must start to invest in human resources specifically qualified for biomedical research, guaranteeing proper terms of employment and competitive wage levels, on a par with the private sector.

Declarations of intent at International and European Union level are a significant indicator of the interest in DCTs among health product manufacturers, patients, researchers and health authorities. There is of course no denying that Italy, despite its clear excellence in terms of originality and spirit of innovation, often shows an unfortunate tendency to fall short of the mark and finds itself pushing back to "pending" status innovations that other countries have already been able to implement. It is important that this interest should act as a stimulus and a warning for Italy too, prompting speedy initiatives in order to promote and regulate this new methodology for conduct of clinical trials to avoid the risk that, while other countries will be involved in DCT, Italy will be select only as "control arm".

Disclosures

Conflict of interest: The authors declare no conflict of interest.
Financial support: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.
Authors contribution: All authors contributed equally to this manuscript.

References

1. Gussoni G. Implementing Decentralized Clinical Trials in Italy: why and how? Multistakeholder expert opinion on priorities for methodology, regulatory affairs, ethics and training. Tendenze Nuove, Special Issue 2/2022 Online (Accessed December 2022)
2. Trials@Home Centre of Excellence Remote Decentralised Clinical. D1.1 First set of recommendations for RDCTs (to be implemented in the pan-EU pilot RDCT) (Version 1 August 2020) Online (Accessed December 2022)
3. Orri M, Lipset CH, Jacobs BP, Costello AJ, Cummings SR. Web-based trial to evaluate the efficacy and safety of tolterodine ER 4 mg in participants with overactive bladder: REMOTE trial. *Contemp Clin Trials*. 2014;38(2):190-197. CrossRef PubMed
4. Gabbrielli F, Zibellini M, Triola R, Bocchino M. Decentralized Clinical Trial: nuovo approccio alla sperimentazione clinica per facilitare il paziente e velocizzare la ricerca. Rapporti ISTISAN 2022| 4IT. Online (Accessed December 2022)
5. Patil B. DCTs deliver big ROI. 2022. Online (Accessed December 2022)
6. Accelerating Clinical Trials in the EU (ACT-EU) Online (Accessed January 2023)
7. Swedish Medical Products Agency. Decentralised clinical trials. 2021. Online (Accessed December 2022)
8. Danish Medicines Agency. The Danish Medicines Agency's guidance on the implementation of decentralised elements in clinical trials with medicinal products. (Version 2.0, September 2021). Online (Accessed December 2022)
9. Swiss Medic – Swiss Ethics. Decentralised clinical trials (DCTs) with medicinal products in Switzerland. (Version 1.0, 09 September 2021) Online (Accessed December 2022)
10. European Commission and European Medicines Agency. Guidance on the management of clinical trials during the COVID-19 (Coronavirus) pandemic – Version 5, 10/02/2022. Online (Accessed December 2022)
11. AIFA notice (update of the AIFA notices published on March 12, 2020) – Clinical trials' management in Italy during the COVID-19 (coronavirus disease 19) emergency (version 2 of 7 April 2020). Online (Accessed December 2022)
12. Petrini C, Mannelli C, Riva L, Gainotti S, Gussoni G. Decentralized clinical trials (DCTs): A few ethical considerations. *Front Public Health*. 2022;10:1081150. CrossRef PubMed