



Clinical Trials: The History, The Pandemic, The Future – What’s Next?

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Introduction

In modern day science clinical trials are pivotal part of the discovery of new medicines. Testing of medicines in animals followed by trials in humans are mandatory part in the process of collection of data for marketing authorization procedures [1]. Clinical trials are the ground for evidence based medicine /where – and/ clinicians must use /only/ published data from clinical trials for decision-making in their practice [2].

In general, the knowledge in medicine goes back to the ancient cultures when numerous theories on the origin of illnesses were present [3]. Many have heard the story of English doctor Lind who found citrus fruits to have positive impact on the course of scurvy by experimenting with variety of diets for his patients. A publication from 1948 describes an experiment for treatment of tuberculosis consisting of two groups of patients: one treated with streptomycin and one with no active

ingredient. The “father” of the randomized controlled trials is today thought to be Bradford Hill who used the random distribution of patients in the treatment groups [2,3]. Nowadays, clinical trials are expanding especially in areas where current standard of treatment does not provide sufficient results, such as oncology, haematology, autoimmunity and rare diseases. Professionals from various scientific backgrounds are constantly in search for the best trial design to answer the predefined clinical question [4]. Long road has been walked ever since Bradford Hill’s first randomization with choice of control group intervention, population criteria, stopping rules, inclusion and exclusion criteria, statistical plans etc. becoming more and more complicated. Randomized controlled trials are on top of the hierarchy of medical evidence but complex designs and multilevel clinical development programs are a new trend for faster accumulation data sufficient for marketing authorization application [5].



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The current article aims at analysing and brainstorming what aspects in clinical trials have changed for good in light of the Covid-19 pandemic. From the perspective of the new European legislation, some future directions for development are pointed out.

The pandemic

Covid-19 had an impact on various aspects of life, one of the most important being health and healthcare systems [6]. A threat to global health such as a pandemic pointed weakness in healthcare, assessment of data and granting marketing approval of new medicines. As clinical trials are mandatory part of the research and development of new medicines and a constantly expanding sector, it would come as no surprise that the pandemic had some significant influence on the area. Regulatory authorities, investigators, research organizations and trials participants all faced different challenges and were urged to amend their work. Some of these changes could represent new aspects of the clinical trial and are worth exploring in order to develop new updated standards, guidelines and working algorithms.

Clinical trials are strictly regulated by numerous international regulations, most important being Good clinical practice (GCP). Clinical trials are expanding worldwide with a foreseen growth with more than 10 billion USD for the upcoming 7 years [7,8]. However, in 2020 Covid-19 changed the paradigm for conducting trials. Balance between regulatory requirements, integrity of trials and safety of subjects is the main challenge for all stakeholders. Regulatory authorities are constantly working towards development of a standard set of requirements for management of Covid-19 in both ongoing and newly started clinical trials. Based on what is already developed by the EMA, with reference to the Good clinical practice, some key aspects are influenced by the pandemic.

What the lockdown has to do with it?

Amidst the outbreak of Covid-19 multiple countries imposed limitations on free movement of people and activities (better known as “lockdown”) [9]. In this context, access to hospitals, trial sites and healthcare specialists was also limited on several occasions. According to the GCP investigational site is a structure of a healthcare institution which is technically equipped to meet the requirement of the clinical trial protocol [10]. In most cases protocol defined visits, assessments and procedures are preferably, if not exclusively performed in clinical trial sites. In light of the limitations driven by the pandemic participants in trials could face obstacles reaching the site and be reluctant to expose themselves to Covid-19 infection. In light of the above, in order to conduct clinical trials, it is reasonable to consider taking them outside the sites in alternative locations or at patient’s home. Medical staff can visit the participants at their home and perform the required assessments, dispense of medicinal products etc. However, some countries are faced with insufficient number of medical doctors and nurses and with the pressure of the Covid-19 infection, sparing time to visit clinical trial participant at home would seem rather unrealistic. The sponsor can outsource activities to third party vendors- for example companies providing home nursing services. In order to meet the requirement of GCP, the sponsor should guarantee that the personnel are suitably qualified and educated on the protocol. Proper documentation and quality monitoring of the process remain crucial. The complication in healthcare access has an impact on monitoring visits which are usually conducted in person. Revision of monitoring plan and postponement of visits are recommended when necessary [11].

Last but not least, in the era of digitalization, online based tools and telemedicine are to be considered. Virtual visits could be the future of clinical trials, especially as technology progress [12]. The main limitation remains the level of computer literacy which if insufficient can jeopardize the success of virtual medicine. In addition, telemedicine visits offer solution only when the protocol defined visits do not include specific procedure or intervention [11,13]. Centralized monitoring on the basis of electronic-based documents and remote data verification are possible with adequate privacy data protection [14,19].

The phenomenon of “avoidable” visits

In general, participants in clinical trials have access to the Investigational Medicinal Products (IMP) via the investigational team. On a scheduled visit to the investigational site an authorized person dispenses new quantity of IMP along with other planned activities and the appropriate documentation. In light of the pandemic however, this approach can be questioned as to whether it is reasonable for participants to visit investigational sites when no assessments are scheduled and the purpose of the visit is limited only to receipt of IMP [19]. In addition, the EMA’s guidance for conduct of clinical trials during Covid-19 advises sponsors not to require participant visit for the sole purpose of re-consent. It is necessary to assess the need for an actual physical visit to the site when no procedures or specific assessments are scheduled. According to GCP informed consent process is conducted in person in the investigational site. Presence of the participant or legal representative is obligatory [10,13]. EMA guidance introduces the term “avoidable” visits where alternative measures should be considered in order to reduce the risk for participants while at the same time stay in compliance with GCP and trial protocols. Such measures may include direct to patient delivery of the investigational product and remote informed consent. Several conditions should be met:

- Use of a licensed courier and a written procedure for delivery.
- Suitable temperature regimen for transportation and storage of the product.
- Delivery of the product, instructions for use and dosage regimen [11].

The direct to patient approach has its limitations as it is not applicable for products which require preparation beforehand, products for intravenous administration or those cases where patient monitoring after product administration is obligatory. Regarding the informed consent process for re-consent an ICF could be sent to the participant for remote signing provided an actual in person consent is scheduled in the first possible moment. An entirely verbal remote informed consent for primary inclusion in trial remains is not recommended.

Overall, the remote conduct is not always applicable. A case by case assessment the protocol requirements and differences between trial phases. For example, bioequivalence studies require frequent blood sampling while in later phases participants are not required to visit trial sites for longer periods of time.

Covid in study protocols

The pandemic created a new reality and it is not possible to neutralize its influence completely. Therefore, depending on the condition and therapy, the approaches for management of clinical trials differ [14,15]. In new clinical trial protocols, Covid-19 is usually included in the criteria for trial population. When par-

Participants get infected with Covid during trial most frequently IMP intake is discontinued until resolution of infection. Personal decision on vaccination should not be limitation nor a condition for participation in clinical trials. The Sponsor is responsible for timely assessment of possible interactions between IMP and vaccines. Guidance for clinical behaviour must be developed and implemented as needed [16]. In order to guarantee safety of participants and integrity of data, thorough documentation processes and safety measures is of pivotal importance [10,13]. Protocol deviations are expected due to the dynamics of pandemic waves and governmental decisions. Clinical trials sponsors and employees must periodically assess data and the need of amendment to the trial.

The growing need for knowledge on corona virus led to the inclusion of sub studies for assessment of Covid-19 infection or vaccine consequences within the main clinical trial protocol. Such secondary studies could provide meaningful information without additional burden to participants.

The future

Despite the pandemic being one of the most significant changes to our reality, other circumstances also define what the future for clinical trials would look like. Within the European Union the sector will change with the new Regulation 536/2014. Like other activities related to medicinal products such as marketing authorization and pharmacovigilance, the assessment of clinical trials will from now on be performed on a community level with a centralized approach. A new European database and informational system (Clinical Trial Information System CTIS) is developed in order to allow sponsors to make one application submission which could be assessed by the concerned member states. In this way the national differences in assessment will be minimized and a new algorithm is introduced. The EU Regulation for clinical trials divides the assessment process into three stages: validation, assessment and decision-making. Similar to the decentralized approach for marketing authorization, in the CTIS for each clinical trial evaluation procedure there will be a reporting member state and member states concerned. Altogether they will assess the documentation and will submit their conclusions. The documentation includes scientific state of knowledge, clinical question, hypothesis to be tested, clinical relevance, goals, endpoints, safety measures, risk/benefit (part 1) and segment on ethical aspects and local feasibility (part 2). Such a differentiation was not present before. Moreover, before CTIS the sponsors submitted the whole documentation in every member state where conduct of trial is planned. Certain aspects like informed consent forms and investigational site and team were adapted according to national legislation. Conclusions and final decisions of the member states also varied because what is allowed in one country could be unacceptable in another.

With the introduction of the CTIS and Regulation 536/2014 the administrative burden will be lightened but in many countries the regulatory authorities would face a whole new set of challenges in relation to the assessment procedure. Active collaboration between countries is a prerequisite for successful start of CTIS. The role of ethics committee will also evolve. In some EU countries there is only one national ethics committee while in others multiple regional ECs are operating [17]. The Regulation will possibly make the gap between work capacity of the committees even more visible as they will play leading role in assessment of part 2 documentation.

Conclusion

Having in mind the lessons learned from the last couple of years, clinical trials will continue to undergo changes on global level. Aside from the EU and Regulation 536/2014, a more flexible administrative procedure is needed in order to offer resolutions to current problems in a timely manner. This includes early recruitment and inclusion of participants, especially in areas of unmet medical needs. In order to facilitate communication between patients and healthcare specialists more digital tools, programs and artificial intelligence platforms have to be developed. As the conduct of clinical trials evolves from site-centered to patient-centered, remote participation may be next great thing, calling for update in GCP. With the new challenges ahead, various professionals will be needed to provide the care and assistance needed to guarantee safe and efficient trials. Professionals, academia, NGOs and regulators should be prepared for all these challenges ahead.

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