Contribution of Methodologies Adapted to Clinical Trials Focusing on High Risk Medical Devices

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Keywords: High Risk Medical Device, Evaluation, Clinical Trial, Adaptive Trial, Bayesian Statistics, Methodology.

Abstract: High risk medical devices clinical trials are complicated, expensive, time-consuming and need an improved clinical evaluation with better scientific evidence throughout the European Union. The purpose of this study is to identify methodologies whose use could facilitate the evaluation of the medical device. Adaptive methods and Bayesian approaches are expert tools that can accelerate access to innovation providing more flexibility but they are insufficiently used because of a lack of expertise and training in the trial community (clinicians, statisticians and regulation authorities). Involving stakeholders (regulation authorities, industrial, clinicians, biostatisticians, end-users) early in the conceptualization of the adaptive design improve adoption, implementation, feasibility and overall quality of that trial.

1 INTRODUCTION

The clinical evaluation of a new medical device is an essential stage in the industrialists' pathway towards market access. The new European regulation (MDR 2017/745) will be fully in force in May 2020 and requires clinical investigation particularly for high-risk medical devices (HRMDs).

Randomized controlled trials (RCTs) have long been recognized as the gold standard for evaluating the effectiveness of drugs. Conducting an RCT takes a great deal of time and financial resources, and great rigour in trying to isolate the specific effect of the intervention under study. Compared with drugs, HRMDs have specific features such as long-term use and unknown interactions with the human body, the means of explanting and replacing implantable devices, the user's skills, the human-machine interface, the management of data-flow generated, etc. These specificities require specific evaluation methods to generate better clinical evidence. Adaptive methodologies have been developed as an alternative to the traditional RCT design.

Even though the legislation, particularly American legislation with the Food and Drug Administration (FDA), qualifies adaptive methodologies as "modern" and "new" methods, a large number of these concepts are old and have remained unused for many years faced with the hegemony of RCTs.

The use of adaptive methods in designing clinical studies has become a major challenge to the evaluation of the safety and efficacy of a medical device, faced with the specificities of the field and the significant financial and temporal restrictions of this industry composed mainly of start-ups and SMEs. To do this it is necessary to find methods that take the specificities of the medical device into account. Several types of clinical studies may be carried out according to the different phases of the device's development.

The clinical phase is generally split into two stages, a first stage of collecting information about safety and performances of the device. This information is collected during feasibility studies or clarifications (implantation technique, patient characteristics, judgement criteria) and a second stage to evaluate the device's clinical efficacy in pivotal evaluation studies to demonstrate the risk-benefit ratio.

This work consists of reviewing methods that may be used in the clinical evaluation of high risk medical devices.

Vidal, C., Beuscart, R. and Chevallier, T.
Contribution of Methodologies Adapted to Clinical Trials Focusing on High Risk Medical Devices.
DOI: 10.5220/0009374503370343
In *Proceedings of the 13th International Joint Conference on Biomedical Engineering Systems and Technologies (BIOSTEC 2020) - Volume 1: BIODEVICES*, pages 337-343
ISBN: 978-989-758-398-8; ISSN: 2184-4305

2 CLINICAL INVESTIGATION

Rather than "clinical trial", the term "clinical investigation" is generally used in Europe in reference to research on medical devices. The expression "clinical investigation" is thus defined in the ISO 14155 norm, "Clinical investigation on medical devices for human subjects", as being "... any study systematically designed and planned for use on human subjects, undertaken to check the safety and / or performance of a specific device." The term "clinical investigation" is defined in a slightly broader way in the American regulations (42 USCS § 1320a-7h (e)) as being "any experiment involving one or several human subjects, or products arising from the human body, and in which a drug or medical device is administered, dispensed or used."

Clinical investigations are subject to scientific and ethical examination. The protocol for clinical investigation includes justification, objectives, design, methodologies, control, how to conduct the clinical investigation and the documentation relative to results and the analysis method concerning it. The level of evidence of a study is characterized by its capacity to answer the question being asked. The randomised controlled trial is the experimental plan that offers the highest level of evidence to demonstrate the efficacy of a device relative to a gold-standard therapy. However, certain specificities of medical devices make this type of trial difficult to perform.

The main limits of resorting to a randomised controlled trial for medical devices are the impossibility to randomise patients, the device's short life-cycle, the small size of the target population, the difficulty of double-blinding, the low acceptability of patients and practitioners, the choice of comparator and the operator-dependent nature of the medical device.

Besides, classical trials are often long, which is incompatible with the evaluation of the medical device whose life-cycle is short and this can hinder access to innovation. When the trial is non-conclusive, this leads to the inclusion of lots of patients in a pointless trial with inefficient treatment. When the trial is conclusive with a very effective device being tested, this poses the problem of patients in the comparator group not having the chance of access to progress and delayed access to progress.
For medical devices designed to compensate for handicap, there is a potential loss of quality of life for the patients who might be able to benefit from them.

Clinical trials may be expensive and this deters certain small and medium-sized medical device companies which, in turn, delays or prevents access to new technologies and medical progress for patients and users. It is therefore essential to find new methods of clinical investigation centred around all these issues.

3 ADAPTIVE METHODS

3.1 Guides

The first part of this work consisted of gathering all the available guides in the field of clinical evaluation of medical devices, and publications on that theme. The following works were used:

- ✓ Methodological choices for the clinical development of medical devices; HAS evaluation report dated October 4th, 2013.
- ✓ Methodological specificities of the clinical evaluation of a connected medical device (CMD); HAS report on the elaboration of the guide on the specificities of clinical evaluation, in view of its access to reimbursement dated January 29th, 2019.
- ✓ Bernard A, Vaneau M, Fournel I, Galmiche H, Nony P, Dubernard JM. Methodological choices for the clinical development of medical devices. Med Devices (Auckl). 2014 Sep 23;7:325-34.
- ✓ Guideline on clinical Trials in small populations; Committee for medicinal products for human use on 27 july 2006.
- ✓ Guidance for the use of Bayesian Statistics in Medical Device Clinical Trials; Guidance for industry and FDA Staff on February 5, 2010.
- ✓ Adaptive Designs for Medical Device Clinical Studies, Guidance for Industry and Food and Drug Administration Staff, Document issued on July 27, 2016.

3.2 Improve Acceptability by Doctors and Take into Account the Operator-dependent Nature

When one arm in the study is less attractive than the other, studies may be carried out according to a Zelen plan or according to a complete cohort pattern. These types of trials introduce flexibility in the attribution of treatments and allow better acceptability of the randomisation by the patients and also give us the possibility of adjusting the results to the randomisation.

Zelen Plan (Zelen et al., 1983, Zelen et al. 1990)**:** The patient's consent is only requested for the new treatment and not for the gold-standard treatment

(simple consent). It is also possible to ask the patient randomised to the experimental group what treatment he/she wants to receive and to give him/her that treatment, or even in each arm of the randomization, ask which treatment the patient would like and to give the patient the treatment he/she wants to have (double consent).

The patients are analysed in the groups to which they were initially randomised and not in the arms of the treatment being received. This plan is only valid if there is not too great an imbalance between groups; that is to say, few patients leaving the study (if these are not related to the treatment) and if the changes of are not very frequent (fewer than 10% of patients changing arms).

This type of pattern might be useful in the high risk medical device area particularly when the target population is small and you think the recruitment is going to be very difficult as in the case of studies focusing on an implantable device (implanted for a more or less long duration, possible withdrawal / difficult withdrawal / very difficult withdrawal / impossible withdrawal) or an invasive surgical technique with a less invasive or less restrictive reference arm (with a drug alternative for example).

Comprehensive Cohort Study (Kearney et al., 2011, Torgerson et al., 1998)**:** the pattern consists of randomising all patients eligible for research and, at a second stage, given the patients who refuse randomisation the treatment they refer. In methodological terms the main pitfall concerns the absence of group comparability. However, it is possible to adjust the results on the randomisation.

3.3 Improve Acceptability of Doctors and Take into Account the Operator-dependent Nature

When certain centres only use one of the two techniques under study and do not know the other technique or only master the one technique and the result is operator-dependent, it is possible to use a trial based on expertise or a cluster trial (or a Stepped Wedge Cluster trial) to increase the participation of doctors and the reliability of the evaluation.

Trial based on Expertise (Devereaux et al., 2005)**:** in this case the patients are randomised to the doctor or team that masters the intervention or technique (for example, prosthetic hip implant surgery). The doctor only performs the procedure he fully masters. In this case, the doctor is device user and he is directly involved in evaluating this. For each study arm, the doctors master the technique that they are going to use and have reached the technical plateau, which avoids any imbalance between the two groups of the trial during the evaluation and is also more ethical. This type of trial is still little used. It is very pertinent when the techniques are different and complex.

Cluster Trials and SWCs (stepped wedge cluster) trials (Barker et al., 2016)**:** With this type of trial, groups of individuals are randomised (hospitals, services, care units, doctors) and not individuals. SWC trials are suitable when you want to gradually implement a new strategy or a new technique without going back to the previous one.

Centres start with the gold-standard technique and the time when each centre switches over to the new technique is randomised. The group experimenting the new technique can be compared both to itself based on the initial measures performed on that group and with the measures from the other patients who are using the gold-standard technique (independent, homogeneous control group).

This type of design may be useful when evaluating a new device, a new technology which is to be gradually introduced (for example a new device which is too expensive to use over several centres in the same area) but the number of clusters must be sufficient to ensure sufficient statistical power and the participation of centres/ services/ doctors must be good especially as these trials may be long (monitoring of inclusions and motivational strategy to be established on the scale of the cluster).

3.4 Compensate for a Small Target Population

When the target population is small, it is important to optimise and maximise the information collected on the patients in the study. In some cases, it is possible to test several strategies on the same patients.

Cross-over Trial (Fuehner et al., 2016, Haddad et al., 2010)**:** In this type of trial, each patient receives two study treatments (or more according to a factorial design). A weaning period is provided for after the patient has been given the first treatment. It is the order of administering the sequences of treatment that is randomised. This type of design is suitable for stable pathologies and when judgement criteria can be read independently over the two periods. The interest of this type of design is divide by at least two the numbers planned for the trial and therefore reduce the duration of the trial. This type of trial may be proposed in cases of evaluating high risk devices whose installation and use are not operator-dependent or if the technical plateau has been reached for all the investigators before setting up the trial.

SnSMART Trial (Small n Sequential Multiple Assignment Randomized Trial) (Tamura et al., 2016, Wei et al., 2018, Meurer et al., 2017)**:** This type of trial can be used when a patient is likely to receive several therapeutic sequences until he/he achieves the treatment aim (complete recovery, remission, etc). The sequences are predetermined beforehand and at the end of each sequence the randomisation is adapted to orient patients either to pursue their ongoing treatment if the response is favourable or to use one of the alternatives being tested in the event of non-response. The number of arms being tested may be adapted, if an arm turns out to be ineffective, it can be removed. These trials potentiate the numbers and may be used in cases of pathologies focusing on small target populations (SnSMART). This type of trial is interesting because it uses the information from the different sequences to compare therapeutic strategies and leads to the inclusion of fewer patients.

3.5 Introduce Flexibility to Take Technological Evolution into Account and Accelerate and Optimise Clinical Development

In order to take technological evolution into account and accelerate clinical development and product launching whilst allowing early terminations (futility/efficacy) or protocol adjustments (evolution/suppression of an arm), it is possible to use tracker design trials, sequential trials, MAMS trials and adaptive trials (detailed further on).

These trials rely on planned intermediate analyses which allow the investigator to glean information which is useful for adapting the development strategy. They are particularly interesting in the context of clinical evaluating medical devices.

Tracker Trial Design (Lilford, et al., 2000)**:** This type of trial was proposed to evaluate new technologies. The principle consists of following the evolution of the technology in the trials based on flexible protocols without a duration of numbers fixed beforehand and based on information obtained during intermediate analyses. It is therefore possible to interrupt a trial early on if the technique is efficient, detect poor performances and guide new developments.

Sequential Trials (Hamilton et al., 2012)**:** The principle of sequential trials consists of planning intermediate analyses in order to be able to conclude early on. The conclusion focuses either on the very high efficacy/tolerance of the experimental arm compared with the control arm if the results observed on the first patients are very promising, that is to say, beyond what was initially expected, or on its inefficacity (futility) if the results observed are below what was initially expected. With this type of trial, it is possible to quickly conclude on the main criterion.

Multi-Arm Multi-Stage trials (MAMS) (Simon et al., 1985)**:** MAMS trials are used in the context of a medical device's accelerated development plan. In fact in this type of trial, sequential trials are gathered into one single protocol (Redman et al., 2015) (e.g.: several competitive devices with one control arm).

The control group is not obligatory but it is recommended. The attribution of patients to each arm is randomised. The arms which do not fulfil the conditions for minimum efficacy (futility) during the intermediate analyses are removed and only the most efficient arms are retained. The first phase is not directly comparative, the second phase gives us the probability of selecting the best treatment compared with the others and the control arm is used to "estimate" the size of the effect.

4 ADAPTIVE TRIALS

4.1 Principle

With adaptive trials it is possible to modify items in the protocol during the study, based on data collected during the planned intermediate analyses without compromising the integrity and the validity of the study.

With adaptive methods it is also possible to strengthen the clinical evaluation of medical devices by authorising the analysis of lots of evaluation criteria, carrying out several intermediate analyses, early terminations in the event of inefficacity, allocating patients to the most promising arms, re-evaluating the sample-size and, more especially, redefining the target population.

These methods also make it possible to combine the early exploratory phases with the demonstrative phases which may make it possible to accelerate and optimise the development and implementation of innovative devices.

It is also possible with these methods to optimise the feasibility phases and confirmatory phases by, proposing much broader, adaptive feasibility trials leading to better-sized pivot trials or by proposing adaptive confirmatory trials testing several hypotheses as required, which would reduce the number of feasibility studies throughout the course of the product's development.

Group sequential design and adaptive sample-size adjustment were used frequently to make study

durations shorter and include a smaller number of subjects.

These methods may therefore make it possible to reduce the requirements in terms of resources, time necessary to finish the studies and increase the chances of the study's success.

There are several possible types of adaptation.

4.2 Response-adaptive Randomization Trials

The aim of this type of pattern is to treat a maximum number of patients with the best treatment under trial and to minimize the number of subjects necessary in the trial by introducing the possibility of an anticipated stop.

It may also be used in trials with several arms. It involves first randomising the patients with a balanced ratio then, gradually and throughout the trial, based on information gathered during the intermediate analyses it is possible to modify the affectation ratio in order to orient more patients towards the most effective treatment (Jiang, F, et al., 2013).

This type of design is an alternative to the multi-stage multi-arm (MAMS) trials seen above (Wason et al., 2014, Wathen et al., 2017).

4.3 Sample Size Reassessment Trial

At the time of the intermediate analyses it is possible to re-evaluate the number subjects necessary for the rest of the trial if the effect observed seems less than what was expected at the beginning of the trial (Magirr et al., 2016).

A misspecification of the expected treatment effect may result in an underpowered or overpowered trial. In the flexible framework, the remainder of a design can be modified at an interim analysis.

In an adaptive trial it is therefore possible to recalculate the number of participants and to increase the power of the trial based on new hypotheses without compromising the validity of the study.

4.4 Seamless Trials

These are trials for which the feasibility and pivot phases follow on from each other in the same trial (Thall, 2008). The two phases are based on complementary criteria (for example: survival without progression and overall survival).

Certain arms can be removed due to inefficacity and only the most powerful arms are pursued in the pivot study.

One control group may be included at the beginning of the pivot phase or before it.

4.5 Adaptive Enrichment

These are trials for which we observe, during an intermediate analysis, a better response to treatment in one of the sub-groups of patients (Simon et al., 2013, Lai TL et al., 2019).

The underlying idea is therefore to study the effect of the treatment in the sub-group whose size is not suitable for analysis beforehand. The eligibility criteria for the trial are modified and the sample-size is recalculated so that the size of the sub-group is sufficient in each arm.

5 BAYESIAN METHODS

5.1 Principle

Bayesian approaches may be used to implement and analyse clinical trials. They are used because they give the possibility of combining information obtained before the trial "prior information" (previous studies, expert opinion, literature…) and information obtained during the trial "current information" to formulate or reformulate a rule for decision-making.

In a Bayesian clinical trial, any uncertainty about a parameter is described according to probabilities, which are then updated during data-collection for the trial. The probabilities are set beforehand based on previous data and the probabilities are estimated *a posteriori* from the data obtained during the trial. There are no statistical tests but the probability of the treatment under experimentation being effective has a 95% credibility interval. However, it is very important that the *a priori* information used does not influence the final result too much (sensitivity analysis required). The quality of information supplied *a priori* is therefore a key element in the credibility of results**.**

5.2 Bayesian Medical Device Trials

Bayesian methods has been supported by the US Food and Drug Administration's (FDA) Center for Devices and Radiological Health for medical device clinical trials and are used in trials on medical devices (Pennello et al., 2008, Campbell et al., 2011, Campbell et al., 2016).

Pennello et al. 2008, explain how these analyses are particularly suitable in this case: "Device trials

can be particularly suitable for Bayesian analysis. For example, if a therapeutic device has evolved in relatively small increments from previous generations of the same type of device, then prior information from the trials of the previous devices can be predictive of the safety and effectiveness profile of the new device (Allocco et al., 2010). The reason the previous trials can be predictive is that the mechanism of action of a therapeutic device is often physical, implying a local effect that is often predictable. In contrast, the mechanism of action of pharmaceuticals is pharmacokinetic, implying systemic effects from similar but not identical formulations, which are often unpredictable. Other potentially reliable sources of prior information for device trials include clinical trials of the device conducted overseas, patient registries, pilot studies, studies of the device on similar patient populations, and perhaps nonclinical studies. Historical controls can also represent prior information for the control arm of a randomized controlled trial".

The information collected beforehand is generally based on previous studies on the same device or on a similar device ideally under similar conditions of use (same technique used, training of similar doctors with the same experience), on the same target population with the same type of management; it comes especially from designers (engineers), users (clinicians, patients) and the academic world (experts).

They are a more flexible alternative to classical methods (frequentist approach). They are used to adapt the randomisation according to the responses observed (see Bayesian adaptive randomisation). These methods also make it possible to compare several sub-groups of patients, several criteria, several time sequences because multiplicity is managed better Bayesian statistics. It is also possible to take missing data into account and to predict an event depending on what has been observed in other patients throughout the trial. The underlying hypothesis is that the patients of a same centre, a same trial or a same group of trials focused on the same device or on a similar device are interchangeable. Meta-analyses also use Bayesian methods to take into account the heterogeneity between trials and between groups of trials (for example several versions of the same device).

6 DISCUSSION

In this review, we noted that there have been many adaptive methods for decades, but their use is recent and mainly in the pharmacological area. Adaptive methodologies have most often been used in oncology.

Adaptive methods may respond to the specificities of clinical investigations on high risk medical devices. Nevertheless, so far they have been very little used in that area (Ribouleau et al., 2011) even though a few published examples can be found in the literature. This observation may also come from a more general situation concerning medical devices which most of the time are released without having undergone a proper clinical investigation. And even though since 1993 the European ruling has mentioned the obligation for each new medical device, whatever its risk category, to undergo a clinical evaluation to obtain CE marking, few clinical studies are indexed before they obtain the CE mark in Europe.

These "new" methods have encountered many suspicions, and the regulatory authorities in charge evoke methodological failings or data-collection problems specific to adaptive designs, which delay the process of product approval. The FDA and the EMA have had mixed experiences with adaptive designs (Collignon et al. 2018, Elsäßer et al., 2014).

Experiences have shown that applicants need to meet early and often with regulators. Adaptive design and Bayesian clinical trials need to be prospectively designed and require extensive pre-planning and model-building from the prior information to mathematical modeling.

Involving regulation authorities early in the conceptualization of the adaptive design improve adoption and implementation of that trial.

Adaptive design and Bayesian clinical trials require highly technically trained statisticians and programmers. A particular pedagogical attention should therefore be paid to accustom all the stakeholders, and particularly the scientists in charge of regulation before and during these trials, to these new uses of new methodologies.

7 CONCLUSION

Overcoming methodological difficulties in conducting clinical trials is a major challenge. Barriers encountered in the field of medical devices lead stakeholders to use new methodologies.

Adaptive methods could be used and has been the subject of several recent reviews (Bothwell et al., 2018).

Besides, various studies explored specific aspects of adaptive trials (Guetterman et al., 2017), including attitudes and opinions regarding confirmatory

adaptive clinical trials and obstacles to using them (Meurer et al., 2016, Guetterman et al., 2015).

ACKNOWLEDGMENTS

We wish to thank Teresa Sawyers, Medical Writer at the B.E.S.P.I.M. for translating this work into English.

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