Exloration of High Risk Medical Devices Methodologies for Optimized Evaluations

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Abstract: Medical devices are developed by manufacturers that need to provide proofs of safety, efficacy, efficiency. In the same time they could be specialists in the technologies, they could not be necessary experts for the targeted medical field and need to be surrounded to build the correct clinical evaluation strategy. Skills required are specific to these particular instruments, and need to be optimized and innovative, as there is as much different devices than the start-ups in the arena. Even if works are performed on the methodological aspects since years, we propose to state a snap of the situation thanks to clinical trials databases exploration, with the aim to extract typical cases for future help and support for the actors. The current article offer to present our strategy of work as well as first quantitative results.

1 INTRODUCTION

In Clinmed special session of Biostec 2020 in Malta, we discussed the adapted methodologies for medical devices field (Vidal, 2020), which is characterized with specificities well documented, on the subjects of randomization, comparator, blinding, acceptance, or endpoints selection… French Haute Autorité de santé (2013: https://www.has-sante.fr/jcms/c_1696842/en/methodological-choices-for-the-clinical-development-of-medical-devices), as well as American Food and Drug Administration (2016, https://www.fda.gov/media/92671/download) for example underlined these points since years.

In Europe, the European commission adopted in 2017 an updated regulation on medical devices EU MDR 2017/745, and on in vitro diagnostic medical devices EU IVDR 2017/746, repealing previous directives (https://ec.europa.eu/health/md_sector/overview_en).

Guidance documents are developed to help actors for implementation of these directives, previously Meddevs, going onto updated Medical Device Coordination Group: https://ec.europa.eu/health/md_sector/new_regulations/guidance_en.

The general context have been related in previous Clinmed sessions -and will be also debated in other articles of this session. In a synthetic approach, we can observe an updated framework around medical devices requiring more clinical evidences, through clinical investigations conceived, realized and analysed with independent medical and clinicians experts, high risk medical devices being the main impacted by these considerations. The way a technological innovation needs to be evaluated being different that the historical well-known ones drugs.

We propose then to:

- formalize an analysis of the registered studies mixing high risk medical devices and interesting methodologies,
- discuss the quantitative results,
- analyse the studies retained in our approach,
- ultimately, we will try to sort out and propose some recommendations for the actors.

In the present paper and to match with the pedagogical objective of the Clinmed session we will focus on the strategy of research and present the first quantitative results, the final report being planned for 2021.

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2 EXPLORATION STRATEGY

In this aim to explore the methodologies adapted to medical devices, we follow a the work from Vidal 2020, and Pruniaux 2021.

2.1 High Risk Medical Devices

The definition of high risk medical devices join the classical criteria defining the classification linked to the level of risk of each device (from I, IIa, IIb, to III), but can not be only reduced to.

European commission even recently open a call in the Horizon 2020 framework, named "Developing methodological approaches for improved clinical investigation and evaluation of high-risk medical devices" (https://ec.europa.eu/info/funding-tenders/opportunities/portal/screen/opportunities/topic-details/sc1-hco-18-2020), without using namely the "class" reference to continental regulations.

Brunotte (2020) add notions of delicate targeted anatomical area, implantability character, or novelty in the technology or the material used.

Following a work performed by Pruniaux et al. in summer 2020 that defined an algorithm (Matlab and Scilab softwares) allowing to search occurences of keywords in databases, we use the same key-words mixing the aspects of implantability, risk in morbidity/mortality, adverse event and misuse risks.

2.2 Methodology

In the same way and following the work of Vidal 2020, we extend her research focused on adaptive methodologies, with the concepts of : Zelen randomization (Zelen et al. 1990), adaptive design (response adaptive randomization, Jiang, F, et al., 2013, or adaptive enrichment, Simon et al., 2013, Lai TL et al., 2019), cross-over, flexible design, sequential trial (Hamilton et al., 2012), treatment switching, sequential multiple assignment randomized trial (SMART) (Tamura et al., 2016, Wei et al., 2018, Meurer et al., 2017), multi-arm multi-stage trial (Simon et al., 1985), stepwise multiple arms, cluster trial, tracker study (for fast technology evolution, Lilford, et al., 2000), Bayesian approaches (Pennello et al., 2008, Campbell et al., 2011, Campbell et al., 2016), sample size reassessment (re-estimation/adjustment) (Magirr et al., 2016), or trial without informed consent or within cohort (Kim, Weijner 2018)…

3 RESULTS

Our first researches focused on https://www.clinicaltrials.gov/ database. The explorations allowed to detected the defined keywords in brief titles, official titles or brief summaries/detailed descriptions.

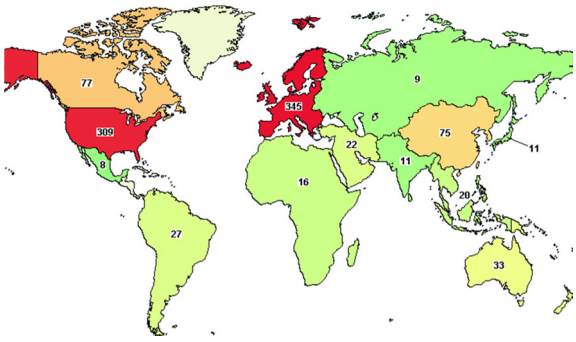

Figure 1: Repartition of the studies concerning high risk medical devices and specific designs (source: map tool of https://www.clinicaltrials.gov/).

We observed 7155 studies on high risk medical devices. With methodology key-words, we detected 61156 studies. Crossing high risk + methodology key-words, we obtained 859 studies.

On this total of 859 trials (on date November 25th, 2020) matching both, 341 were completed, 14 withdraw, 1 suspended, 54 not yet recruiting, 142 with results, 130 accepting healthy volunteers, 6 with usability key-word.

A quick overview of the map provided by clinical trials website presents that these kind of studies are ainly performed in Europe (345), North America (309+77), and to a lesser extent in India (75) (figure 1).

We can also observe an evolution in terms of number of concerned studies (figure 2), with 16 referenced before 2001, and a regular increase (105 in 2020).

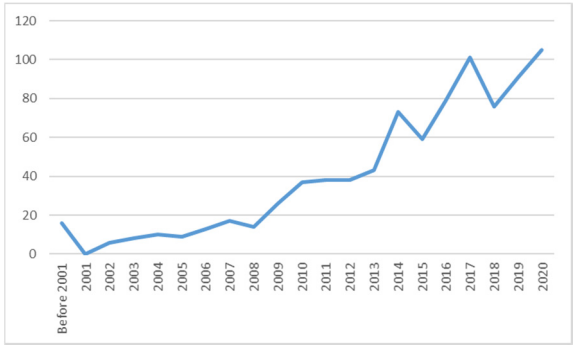

Figure 2: Evolution of trials on medical devices involving specific methodologies, over time.

Table 1 present also the distribution of the different methodologies in the obtained results.

Table 1: Repartition of methodologies in the identified studies: at least one key word concerning methodology – some could have more than one, that is why we get here a total of 933.

Type of methodology	Number of concerned studies
Cross-Over	259
Trials within Cohorts	162
Flexible	132
Randomization Adjustment	124
Sequential	86
Adaptive	62
Trial without Informed Consent	46
Cluster	28
Treatment Switching	13
Tracker Study	7
Bayesian	6
Sample Size Adjustment	3
Dose Finding	2
Tracker Trial	2
Stepwise Multiple Arm	1

We performed the same extraction on Medline (https://pubmed.ncbi.nlm.nih.gov/), with article type filter "clinical trial":

- we detected 10380 publications on high risk medical devices,
- with methodology key-words, we obtained 88560,
- crossing high risk + methodology key-words, we observed 864 articles (still on November 25th, 2020).

4 NEXT STEPS

4.1 Selection of the Studies of Interest

The selection phase will consist in defining criteria allowing to retain relevant studies.
We will rank the trials by type of methodology.
The brief titles, official titles, then details of the studies will be successivelly read by two experts; a consensus will be reached on the retained trials to be explored and retained in our discussion.
Criteria of selection will focus on the fact that the study addresses well an high risk medical device (the definition is not exactly shared), and that an "innovative" / interesting design was provided; the first identified methodologies will be discussed in order to determine the originalty and relevancy for medical devices field.

4.2 Analysis

In term of analysis, we will considerate the possible problems, challenges, key points or strong points enhanced by the investigators: we will pay attention to the duration of the study compared to the planned duration: was the study performed until the end? If yes, quicker or slower than planned? If stopped, what was the reason ? Devices was in question ? Was there any discussion about the relevancy of the choosen methodology ? ...

We will also extract the possible usability information that could be detected with specific methodologies, usability that is well know to be important for considerations on technological innovations.

For the results published, we will explore these information thanks to https://pubmed.ncbi.nlm.nih.gov/ website and based on our first articles selection, to see if the extractions between the registrered studies and the publications of the results match, and in which way they are complementary or different. We could have there an interesting view of the ability of the available data to provide enough information compared to our hypothesis. Are the documentation provided in Clinical trials or publications results systematically sufficient for confirming our questions.

4.3 Extension to Other Databases

We plan to test the same strategy on adapted algorithms for Medline website, Cochrane library (https://www.cochranelibrary.com/), or databases for clinical trials performed in other part of the world (example in Asia: http://www.chictr.org.cn/abouten.aspx, https://www.umin.ac.jp/ctr/).

5 PERSPECTIVES AND PRACTICAL CASES

Mixing quantitative and qualitative analysis (looking onto details inside the studies), we will then considerate the state and number of employed methodologies, depending of the device evaluated as well as its stage of development.

Based on our experience, we extracted few illustrations allowing to provide an idea of possible typical cases and the way evaluations could be provided to adequatly answer to requirements from between authorities (for market assess, for studies

approvals), industrials, scientists and cliniciens, and for sure patients.

5.1 A Device without Assess to Market Approval

In our practice, we had the case on which the strategy of market acess was different depending of the country/area of the world on which the manufacturer would like to apply, which underlined different procedures, but also lectures by authorities concerning the way a device need to bring proofs.

5.2 A Software without Assess to Market

The european regulation address specific sections for software, that could have strong impact in the diagnosis or care of the patients.

We can meet the case on which industrials selected the strategy to play on some edges (or adaptations?) in the lecture of the regulations, that permit them to diffuse an "inoffensive observational" version of their device onto hospitals and clinics on very early phases; in that way, the aim consists in aggregation of data, without any intervention on patients. The data accumaleted need for sure to comply with General Data Protection Regulation (GDPR https://gdpr-info.eu/), but could help the manufacturer to adapt its future device (especially in machine learning/artificial intelligence considerations), and to feed his future FDA or CE mark with in fact data provided by the real life.

Another example relies on a software for which we were involved since its very early stage for development; the manufacturer had no experience and was not structured for medical devices field. In order to well understand the context, as well as giving time to adapt the device and securize the things before going on patients, we structured a two sequences study, the first one being dedicated to observe the current practices (without the software) and to define the scenarii of use, the second one introducing the software in simulation experimentation.

The regulatory positionning could then go on a software first dedicated to training of caregivers, before going on a high risk / class III medical device - if enough proofs accumulated in these simulated envirmnements.

5.3 A Device with a CE Mark

On medical devices already on the market since years, we had to provide specific medico-economic evaluations, taking into account these efficiency considerations, in terms of duration of hospitalization, back to work time, quality of life… And in fact impacting the way the care and the evaluations need to be arranged, with sometimes a strong gap between what imagine the industrial at the very beginning, and the proposed organization.

5.4 Use of Real Data

More and more and with the available big amount of data, it is possible to imagine some "virtual" controlled group, with possible pairing between a real patient prospectively enrolled in a study, and his pair selected onto database. This need strong thoughts on criteria of inclusion (pairing), as well as available data linked to the criteria of judgements. And then even if it's seems quite interesting (reducing the number of patients involved in a research, gaining time, reducing cost of a study…), it is not possible in many cases and must not make forget to respect the chronological steps of testing.

5.5 Implementation of a Device along the Trial

For a very diruptive innovation involving not only technology, but also organizations around patient and its environment, we can pay attention to a tracker trial that in fact allowed different phases introducing implemented version of a prototype, each phases turning profit from the previous ones, and feeding the next ones (in term of adaptation of the device, but also for the evaluations).

6 CONCLUSION

Considering our results, we plan to extend analysis and to in end build recommendations, illustrating and guiding the skateholders on the pathway to the selection of a relevant methodology, depending of the device, its level of risk but also its destination, its use, or its stage of development. We will also think about a "bottom up" approach by starting from the methodology/design point of view.

We built a working group constituted of methodologist, medical doctors, specialists in medical devices evaluations, usability experts, in order to set up this identification and study of cases. Our results will be confronted to different actors of the field, disseminated and adapted along the feedbacks we'll received, and finally to provide better

evaluations, better medical devices, for better healthcare for patients.

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