UNIVERSITÀ DI PISA

DIPARTIMENTO DI INGEGNERIA DELL'ENERGIA DEI SISTEMI DEL TERRITORIO E DELLE COSTRUZIONI

RELAZIONE PER IL CONSEGUIMENTO DELLA LAUREA MAGISTRALE IN INGEGNERIA GESTIONALE

HTA for Medical Devices: a literature analysis and a case study

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Sessione di Laurea Magistrale del 27/09/2023

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Sommario

L'Health Technology Assessment (HTA) è un metodo multidisciplinare di valutazione delle tecnologie sanitarie.

Il presente lavoro di tesi si inserisce nella prima fase del progetto "T.H.E. - Spoke 5 - HTA line", che si pone come obiettivo la creazione di uno strumento di mini-HTA per la valutazione dei dispositivi medici.

Nello specifico, il lavoro di tesi ha avuto l'obiettivo sia di analizzare la letteratura al fine di individuare le tematiche principali su cui si è focalizzata la ricerca sull'HTA negli ultimi undici anni, sia di indentificare gli Enti/Aziende Ospedaliere coinvolti nel processo HTA della regione Toscana.

Questo ha permesso di effettuare l'analisi dei processi AS IS di HTA di due dei principali attori regionali - l'Azienda Ospedaliero Universitaria Pisana (AOUP) e l'Azienda Ospedaliero Universitaria Senese (AOUS) - che sarà fondamentale per impostare il protocollo di indagine per i futuri casi di studio.

Abstract

Health Technology Assessment (HTA) is a multidisciplinary method of evaluating health technologies.

This thesis work is part of the first phase of the "T.H.E." project. - Spoke 5 - HTA line", which aims to create a micro-HTA tool for the evaluation of medical devices.

Specifically, this thesis work had the objective of both analysing the literature in order to identify the main topics on which research on HTA has focused in the last eleven years and to identify the Bodies/hospital companies involved in the HTA process of the Tuscany region. This allowed the analysis of the AS-IS HTA processes of two of the main regional players - the *Azienda Ospedaliero Universitaria Pisana (AOUP)* and the *Azienda Ospedaliero Universitaria Senese (AOUS)* - which will be fundamental for setting up the investigation protocol for the future case studies.

1. Introduction

Health Technology Assessment (HTA) is a multidisciplinary process that synthesizes information on the clinical, economic, social, and ethical issues related to the use of a health technology, in a systematic, transparent, impartial, and robust way. The technologies being evaluated can be drugs, medical devices, vaccines, procedures, and, more generally, all systems developed to solve a health problem and improve the quality of life. This thesis focuses on HTA for medical devices (MDs). Since its first application in the United States in the 1970s, HTA has developed rapidly and has been applied globally, becoming the basis for health decisions such as pricing and reimbursement in many different countries and regions. However, more of the existing HTA research concerns medicines rather than medical devices. Medical devices differ considerably from drug therapies in terms of their product lifecycle, regulatory environment, diversity, user–device interaction, and so on (Drummond et al., 2009). Hence, existing HTA guidelines which are mainly focused on drugs, cannot be applied directly to the HTA of medical devices even with adaptation. Another big difference between MD and drugs is the fact that, in many European countries, the decisions to adopt MD are taken by the hospitals that however are left with no guidance as regards decision-making tools able to do it. Therefore, the most used criteria for evaluating a medical device at the hospital level are the cost of the device and the presence of supporting scientific literature. Regarding the cost, it is usually evaluated as the immediate purchase cost without considering the cost savings resulting from the use of the medical device. Regarding the scientific literature, there is often no solid foundation, especially for innovative devices. Therefore, the need arises for a tool that can help the decision-makers in their choices. By intercepting this nascent need, following the recommendation of the European Parliament (adopted by the European Network for Health Technology Assessment - EUnetHTA) to promote the convergence of HTA tools/procedures/methodologies, the "T.H.E.[1] - Spoke 5 - HTA line" project addresses the call for a standardized tool for micro-level HTA for medical devices. The target is to create, within a three-year time horizon, a tool that can be used in the HTA process of the Tuscany region. This thesis describes the activities carried out in the first phase of the "T.H.E. - Spoke 5 - HTA line" project. According to the tasks and deliverables of the first phase of the "T.H.E. - Spoke 5 - HTA line" project, the goals of this work are the following: *i*) a literature analysis, to identify the main topics on which HTA research has focused in the last eleven years; *ii*) the creation of a database with the HTA applications made by Tuscan hospitals; *iii*) the AS IS mapping of the

[1] Tuscany Health Ecosystem

HTA processes of the *AOUP* and the *AOUS* to identify the phase/phases in which the evaluation currently takes place.

2. "T.H.E. - Spoke 5 - HTA line" project

T.H.E. - Tuscany Health Ecosystem, the Tuscan project in the field of innovation ecosystems (promoted by the *PNRR – Piano Nazionale di Ripresa e Resistenza* funds), was born as an aggregation of scientific, technological skills and research infrastructures in the Life Sciences sector. It is one of the 11 nationally funded innovation ecosystems under the PNRR, the only one dedicated to life sciences. T.H.E. was born from a project proposal presented by the University of Florence, as lead partner, in line with one of the strategic guidelines of the Tuscany Region relating to life sciences. T.H.E. activities are divided into 10 sectors or research nodes (Spokes), all related to advanced life sciences topics: **Spoke 5** - Implementing innovation for healthcare and well-being. Spokes 5 and partly Spoke 10 will act as transversal units, supporting the activities of other Spokes (fig. 1).

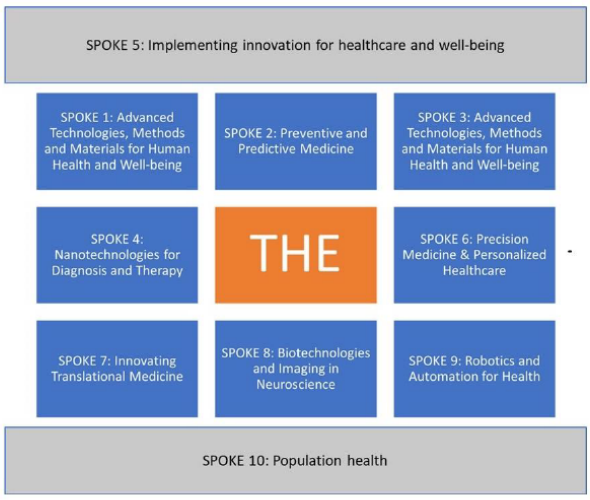

Figure 1 - Spokes structure

Among the possible lines of action present in Spoke 5, the focus is on Health Technology Assessment. The final output of this three-year project is to propose a standardized tool for the micro-HTA with the following characteristics: *i*) a standardized set of criteria that can be used for all devices, whatever their risk class (I, IIa, IIb, III); *ii*) use of the most suitable MCDA technique, according to the suggestions provided by the *Autorità Nazionale Anticorruzione (ANAC)* code of conduct (AHP, ELECTRE and TOPSIS); *iii*) insertion of elements of flexibility (specific criteria) to take into account the specificities of the medical device/context.

3. Literature analysis

In order to identify the most influential streams of literature in the HTA for medical devices' field and its topics' evolution over time, it was decided to carry out a bibliometric analysis by citations using VOSviewers software and a main path analysis using Pajek software. The choice

to carry out a bibliometric analysis was made based on the indications in Donthu et al. (2021), given the large number of input papers and the broad scope of the review.

3.1 Citation Analysis

Citation analysis is a basic technique for science mapping that operates on the assumption that citations reflect intellectual linkages between publications that are form when one publication cites the other (Appio et al., 2014). To realise the citation analysis, it was used the Elsevier Scopus database, with specific inclusion and exclusion criteria: Keywords - "HTA" OR "Health Technology Assessment" AND "Device"; Data Range - publications from 2012 to 2023 (31st March 2023); Language - English; Source Type - Journal; Document Type - Article, Review, Short Survey. To accomplish the analysis, it was used VOSviewer, a software tool for constructing and visualizing bibliometric networks. Figure 2 shows the network visualisation and the primary network visualisation by citations obtained importing in VOSViewer the 509 selected papers.

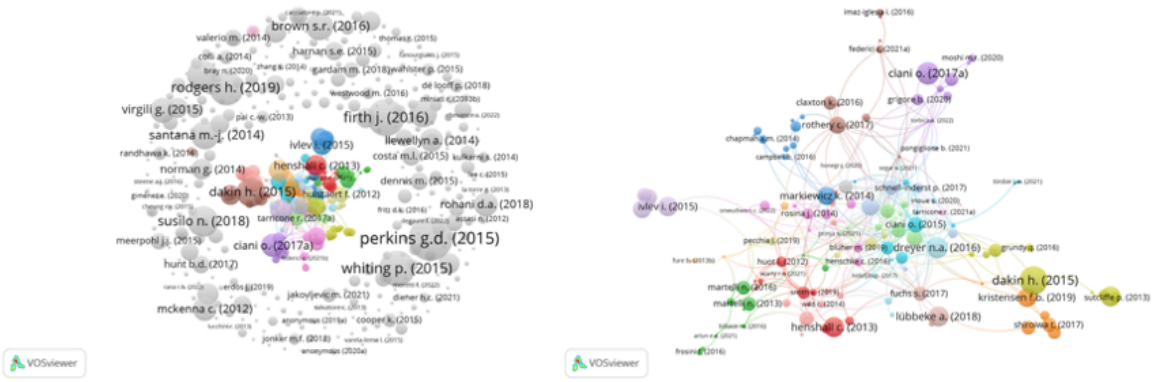

Figure 2 - Network and primary network visualizations

These network visualisations show that most of the papers (368 papers, 72.3% of total papers) are not interconnected by citations (on the left) and there is a primary network composed of 141 papers grouped in 19 clusters (on the right). In the graph, the different colours indicate the membership of the different clusters identified by VOSviewer. In order to get the main topic of each single cluster, it was created this framework to follow (single cluster): Phase 1 - Preliminary analysis of the graph; Phase 2 - Identifying "cite/cited by" connections for each paper[2]; Phase 3 - Identification of article reading priority based on "cite/cited by" connections; Phase 4 - Reading articles with focus on the parts of the text "cite/cited by"; Phase 5 - Broad definition of the main topic of the cluster (with any alternatives and keywords); Phase 6 -

[2] There is no direction of the link between two nodes (papers) of the graph. The year of publication of the articles can clarify this doubt. In the case of the same year of publication, the direction of the link will be explained when reading the article.

Describing the cluster; Phase 7 - Title definition. Table 1 shows the identified research streams of the 19 clusters.

#	Research Streams	#	Research Streams
1	Issues in the implementation of HTA process	11	Challenges in HTA for MDs
2	Decision-making process in Hospital-based HTA (Hb-HTA)	12	Rethinking the assessment of medical devices
3	Early assessment and economic evaluation in HTA	13	HTA as cost-cutting tool
4	HTA for High-Cost Medical Devices	14	MCDA implementation
5	Pre and post marketing evaluation of clinical benefits and European HTA framework	15	Importance of Real-World Evidence (RWE)
6	Peculiarities of the assessment of Medical Devices	16	Issues with DRG-based payments
7	The implementation of HTA practices and international collaborations: Japan vs UK	17	HTA Process harmonization
8	Coverage with Evidence Development (CED)	18	Sui generis HTA in Italy
9	MD unique characteristics with respect to drugs as drivers of specific assessment practices	19	Need for (clinical) evidence-based data
10	Authorization and reimbursement of high-risk medical devices		

Table 1 – Research streams of citation analysis

3.2 Main path Analysis

To perform the analysis, it was used Pajek, a software tool for the analysis and visualization of large networks. The main path analysis helps to identify how the research streams on a specific topic are linked and how the theory evolves during the time window considered. The main path is composed of 14 papers that represent the research flows, from 2012 to 2023, about the HTA approach for evaluating medical devices (fig. 3). Specifically, by analysing the documents belonging to the path, it is possible to build a theoretical background and recognise criticalities and challenges about HTA on MDs using the skeleton papers on this topic. Four different research flows lead to the work of Kovacs et al. (2022) that deals with the transferability assessment issue, i.e., related to the need to transfer the outputs of the MDs evaluations from the European Counties with a rooted HTA approach to that with late technology adoption rate. In this article, it is highly recommended to consider the MDs' clinical and economic value during their assessment and to perform HTA evaluation on a group of devices with the same (or similar) characteristics rather than on a particular device version. All research flows converge in the paper of Torbica et al. (2022) which highlights several gaps related to the HTA of MDs, both practical and theoretical. According to this work, new research should aim to deal with the improvement of MDs evaluation, identify how to access and use real-world data, strengthen the use of economic evidence, use new methods for evaluating digital health technologies (such as the mHealth apps) and performance evaluations at the early-stage of MDs development (starting from the proof-of-concept stage). In the more recent paper belonging to

the main path, the work of Tarricone et al. (2023), the authors underline how the boundaries highlighted by past research related to the MDs evaluation, diffusion, and use in UE remain.

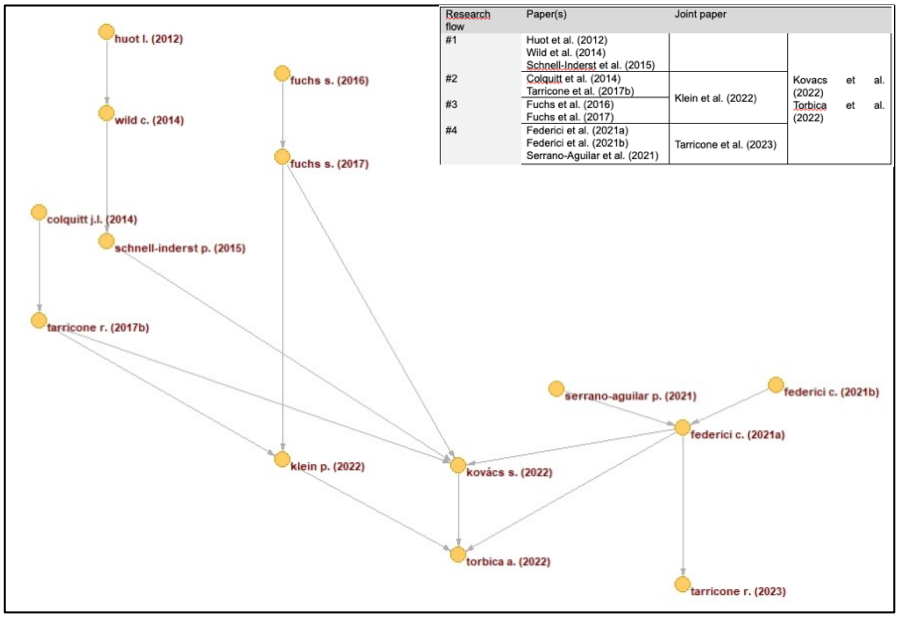

Figure 3 - Main path analysis

Among the topics that emerge from the analysis of the literature, one of the most relevant is the lack of data with which to carry out the evaluations. MDs regulatory system, which makes the device accessible even without the presence of clinical trials, makes the collection of Real-World Evidence (RWE) data more relevant than the experimental clinical data typical for drugs. Another important topic concerns the management problem that characterizes HTA processes: there is a lack of standardized procedures and greater involvement of all stakeholders is necessary (the entire life cycle of the medical device must be considered). Examples of micro-HTA tools in the literature are not numerous, precisely due to the difficulty of identifying the set of criteria useful for evaluation. Often the tools, once created, are used for the evaluation of a single medical device, with the definition of ad hoc criteria (with a survey) for that specific device (Martelli et al., 2016 and Yang et al., 2021).

4. HTA applications in Tuscany

It is possible to see the HTA applications of the various Tuscan hospitals via the specific web page at https://www.regione.toscana.it/-/prodotti-hta. The applications concern high-risk classes (i.e., IIb and III) medical devices. For low-risk classes (i.e., I and IIa) medical devices, hospitals manage the process internally and it isn't necessary to fill in an HTA report.

4.1 HTA Dashboard

The data in the HTA reports were used to create a Dashboard with Excel sheets (fig. 4). This made it possible to have the information necessary to immediately identify the number of HTA

applications, made by each hospital, available on a single screen and to have a ranking of the hospitals to contact for the case studies.

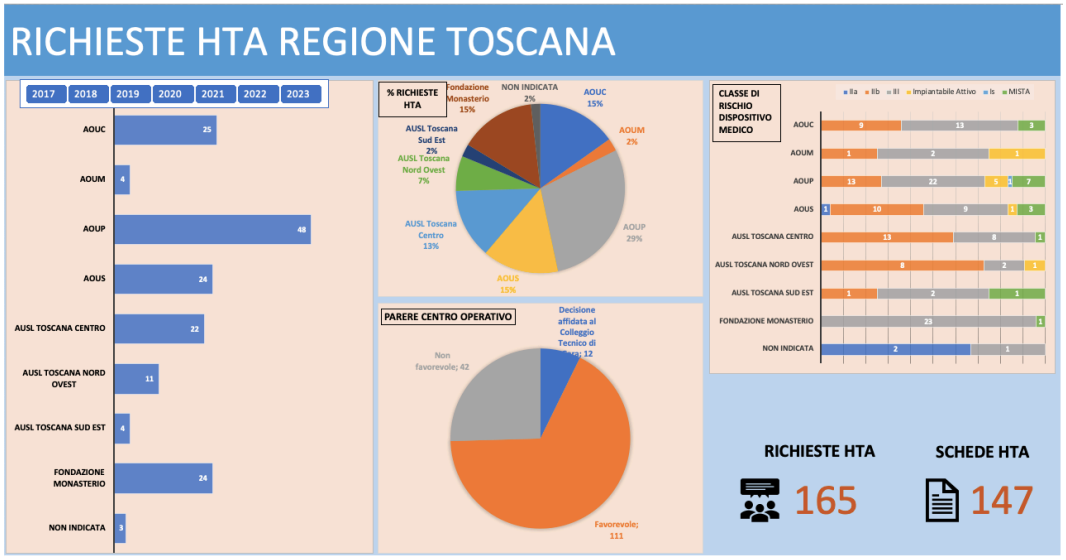

Figure 4 - HTA Dashboard (Tuscany)

The AOUP is the one with the highest number of applications. The data are expressed cumulatively from 2017 (the first year in which the region started producing HTA reports) to 2023 (last update June 5, 2023). By clicking on the top left corner slicer, it is possible to visualize the data relating to each single year[3].

5. Case study

In addition to the hospitals that request a particular medical device, there are three Bodies involved in the HTA process in Tuscany: *ESTAR (Ente di Supporto Tecnico Amministrativo Regionale*), *Centro Operativo (CO)* and *Commissione HTA*. For risk class IIb and III medical devices not yet approved, the clinician fills in an HTA form and sends it to the *CO* for evaluation. Decree n.17610, issued on 7 September 2022, put into operation the *CO*, a structure with various competencies that are not limited to the medical device sector. The *Commissione HTA* carries out the function of implementing the proposals formulated by the *CO* and converting these proposals into operational decisions with relative executive measures. Regarding the evaluation of medical devices required for regular use by a hospital, the assessment process of Tuscany foresees carrying out a preliminary activity with the elaboration of an HTA report by *CO* which can express a positive, conditional/positive[4] or negative opinion on the purchase. The approval or not of the medical device is instead up to the *Commissione*

[3] The number of HTA-submitted applications is greater than the number of HTA reports because several requesting hospital units may be indicated in the same HTA report (in this case the HTA report is not duplicated).

[4] conditional/positive: the purchase of the MD is subject to the satisfaction of some pre-specified conditions, which may include both preliminary experiences of clinical use conducted with products supplied free of charge by the manufacturer, and real research protocols subject to the regulations in force on the subject (including approval by the competent ethics committee and/or interaction, where foreseen, with the Istituto Superiore di Sanità (ISS).

HTA which can implement, modify, or reject what the *CO* proposed. The outcome of the decisions of the *Commissione HTA* is then communicated to all the Health Departments, to all the Company Pharmacies and to *ESTAR*. *ESTAR* manages tenders for medical devices. Starting from August 2022, the HTA reports display additional information regarding the status of an innovative device or not. The attribution of innovativeness to a certain device takes place according to Resolution No. 737 of 06-27-2022[5]. The innovativeness evaluation is made by *CO*.

5.1 AS IS process mapping

It was made the AS IS processes' mapping of two important Tuscan realities, according to their HTA applications numbers in the HTA Dashboard: the *AOUP* and *AOUS*.

In both meetings, members of the *CO* were present. Further meetings are planned for the TO BE process. The focus is on local assessments: how they are done today, by identifying the phases in which the decision-makers act with their evaluations, and how they could be improved.

5.1.1 AS IS AOUP HTA process

The clinician submits a request on *ESTAR* IT portal. This request is communicated to the *AOUP* company pharmacist. The company pharmacist first checks whether the medical device has the CE marking. Subsequently, he/she checks on *ESTAR* IT portal (*ESTAR* database) whether the device has already been approved at a regional level or if there is an already approved alternative that corresponds to the profile identified by the clinician. If so, there will be the purchase through *ESTAR*. For "not already approved" devices, there may be two cases: *i*) for risk class I and IIa devices an internal assessment is carried out and the purchase request is sent to *ESTAR*; *ii*) for risk class IIb and III devices, the clinician, with the collaboration of the pharmacist, fills in the HTA form. This form is sent by the pharmacist to the *CO* and, at this point, the common regional HTA process for all risk class IIb and III devices begins, as described above. Fig. 5 represents the AS IS HTA internal process for *AOUP*.

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[5] The innovative versus non-innovative classification derives from the comparison between the device in question and the previous standard of care and is based on the following three criteria:
1. "Unmet clinical need", i.e. unmet or insufficiently met therapeutic need;
2. Documented benefit of a clinical nature;
3. Documented economic and/or organizational advantage.
This third criterion is taken into consideration only if the device proves at least to be clinically comparable or non-inferior to the reference technologies.
A documented advantage of a clinical nature means that which derives in the order: a) from a randomized controlled trial; b) from an indirect comparison of outcomes, also reported only in narrative terms and possibly referred to historical control cases.
On the one hand, to obtain recognition of innovativeness it is sufficient that at least one of the three criteria is satisfied; on the other hand, and above all regarding criteria 2 and 3, the resolution provides that the device must exceed a minimum threshold of clinical or economic value, defined in numerical terms.
Furthermore, it is important to underline that, upstream of the evaluation of the three criteria described above, the devices must satisfy two evident pre-requisites, i.e. the availability of at least one clinical study published in a journal surveyed by Pubmed and the availability of at least one study reporting an estimate of the incremental benefit in comparison with an adequate comparator.

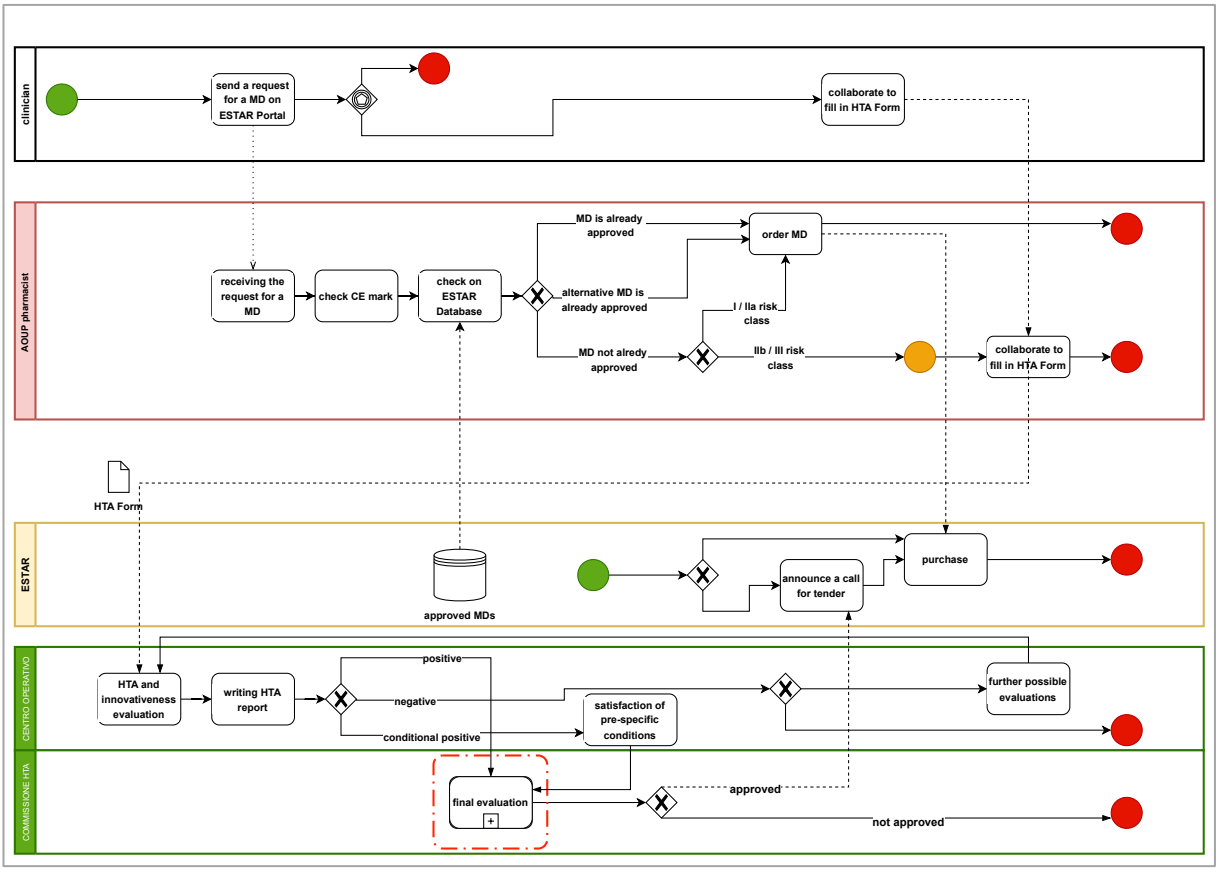

Figure 5 - AS IS AOUP HTA process

5.1.2 AS IS AOUS HTA process

The *AOUS* has an internal HTA structure: the *Unità di Valutazione delle Tecnologie (UVT)*[6]. The different types of medical devices have been divided into five areas: *i*) non-electrical disposable medical devices; *ii*) non-electrical reusable medical devices; *iii*) technologies in service (not owned); *iv*) purchased (owned) technologies; *v*) ICT (health-field softwares). Each area has its own area representative. The area representative receives the requests pertaining to him/her, checks the CE mark, brings them to the *UVT* table on a weekly basis, makes programming, follows the acquisition process up to the delivery of the device, and reports the costs. The process for the evaluation of "already approved", "already approved alternative" and "not already approved" medical device is the same of *AOUP*'s process. In this case, instead of the company pharmacist, there is the area representative. The HTA form is sent by the area representative to the *CO* and, at this point, the common regional HTA process for all risk class IIb and III devices begins. Fig. 6 represents the AS IS HTA internal process for AOUS.

5.1.3 Additional considerations

Single-use MD: usually a single-use medical device (lifesaving) is out of the tender.

[6] The *UVT* is a multidisciplinary team, created with a company resolution in 2019, which carries out evaluation of medical devices

It is an ad hoc device[7] for a specific case and is used as an exception to the acquisitions that are already covered by the *ESTAR* contract.

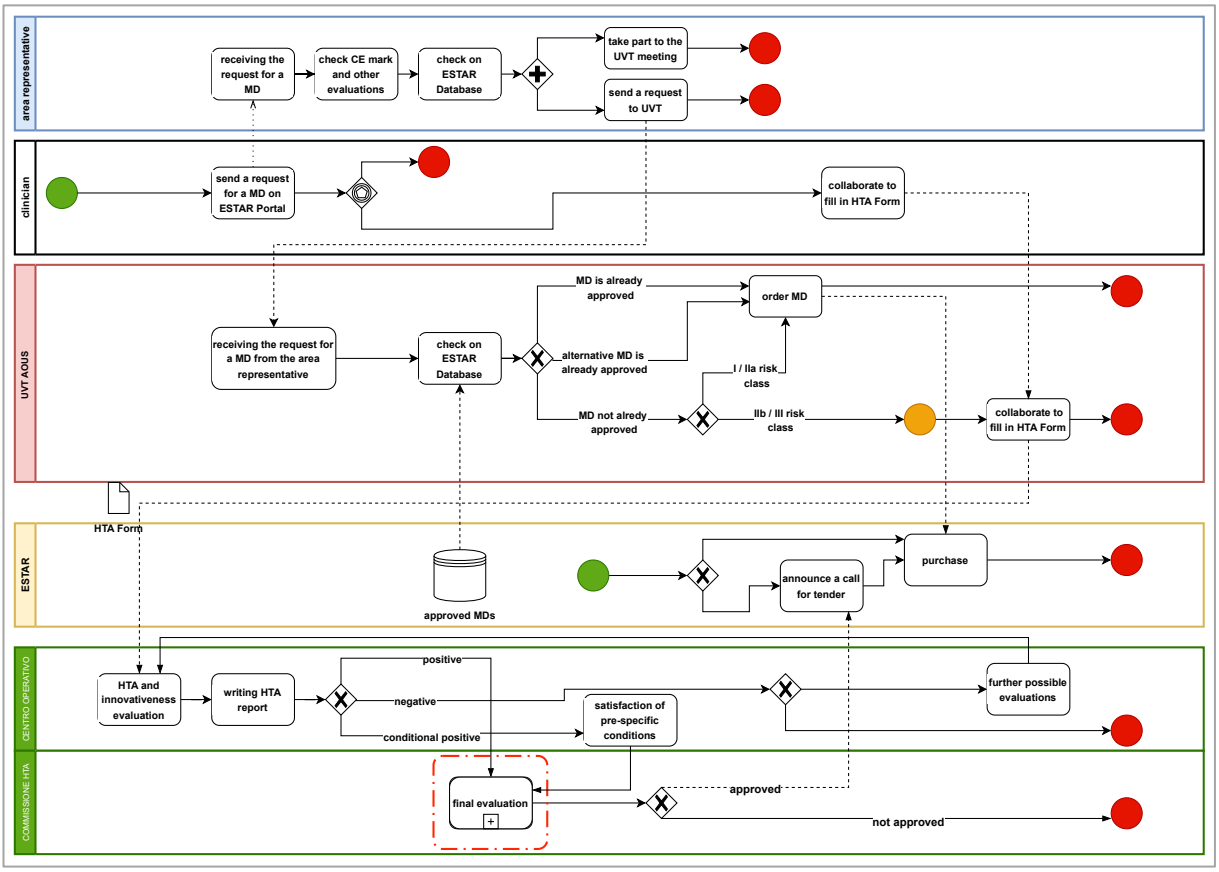

Figure 6 - AS IS AOUS HTA process

The reply to this kind of request arrives within 72 hours. After internal validation by the Health Department, a *Richiesta d'Acquisto (RDA)* is made on the *ESTAR* IT portal, which includes the single case section. The *AOU/ASL* can use the device as a supply on an approval basis; the *ESTAR* codifies the request, opens a dedicated contract with the *Codice Identificativo di Gara (CIG)*, and closes the product (which can no longer be ordered or viewed on the portal by other healthcare companies). **Risk class I and IIa medical devices**: the evaluation is carried out internally by the hospital[8]. **Corporate pharmacist**: the role of the pharmacist is fundamental in the HTA process. He/she communicates with numerous areas: clinical area, Management, Region, ESTAR, management control, and surgical planning. **Final evaluation:** It is not clear how the *Commissione HTA* makes the final decision on whether or not to buy a device. **Medical device as a gift**: with customized report with technical characteristics and CE mark. Its use and possible advantages are evaluated. If considered advantageous, the HTA form is made for risk classes IIb and III.

[7] For a single-use device, a one-page form is filled in with PUBMED literature references (but also, if necessary, using grey literature).
[8] A *Richiesta d'Acquisto (RDA)* is made and sent to *ESTAR* IT portal, with the following pieces of information: clinical evaluation, annual quantity, impact on expenditure, possible reorganization of procedures connected to the device, procedure times.

6. Conclusions

The aim of this work is to: *i*) carry out a literature analysis to identify the main topics in the HTA field; *ii*) understand the HTA process of the Tuscany region with particular attention to some appropriately identified local realities. One of the fundamental aspects of HTA for MDs, that clearly emerges from the analysis of the literature, is the need to uncouple this process from that relating to drugs. Existing HTA guidelines mainly focus on drugs and cannot be applied directly to the HTA of medical devices even with adaptation. There is a need to have RWE to help the decision-maker during the assessment. It is necessary to solve the management problem of HTA processes, by providing standardized procedures shared by all stakeholders involved in the process. Recently it has been possible to find papers that try to identify basic criteria that can be used to create a standardized decisional tool considering the local characteristics of the context where decisions must be made (Tallarico et al., 2020) and articles that suggest recommendations for standardizing the decision-making process (Daubner-Bendes et al., 2021), thus making it easier to take decisions. Regarding the management of the HTA process, as told above, the internal organization of each Tuscan hospital is different, everyone acts in their own way. Both the analysis of the literature and the experience with some Tuscan realities argue in favour of the creation of a tool that can support the decision-maker in evaluations.

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