EUROPEAN COOPERATION
IN SCIENCE AND TECHNOLOGY

COST EMF - MED (Action BM1309):
European network for innovative uses of EMFs in biomedical applications

STSM Report:

Pre-market assessment of EMF interactions and applications: a case study on electroporation

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Abstract:

Health Technology Assessment (HTA) is a multidisciplinary and multidimensional process useful for evaluating alternative and competing medical technologies. HTA of medical devices may be particularly challenging because medical devices effectiveness is strongly depended by factors that are not strictly related to the device but to other factors as its use, the training of personnel, the other technologies available in the surgery theatre and other user-dependent factors, which are not easily captured with standard health-economics models. The goal of this STSM was to identify the main criticisms of HTA of Electroporation and propose a preliminary model for pre-market assessment of this technology.

A. Purpose of the STSM

The purpose of this STMS was to support Dr Leandro Pecchia in spending one week working in collaboration with Prof Miklavcic and his group in order to identify criticisms of Health Technology Assessment (HTA) methods for electroporation applications and to develop a method for the pre-market HTA of electroporation.

B. Work Description

During the STSM the following activities were carried out:

1. factors that could affect pre market health technology assessment (pHTA) of electroporation applications were assessed, including:
    a. technological aspects that can be relevant for the assessment of the effectiveness of this techniques for cancer treatment
    b. procedural factors that can affect the design of proper trials
    c. user issues that can affect the ratio efficacy/effectiveness (effectiveness = efficacy in every day clinical practice)
    d. economical factors that can affect the revenue model
2. a preliminary model for the pHTA of electroporation was proposed

C. Results

Previous researches proved that HTA methods that perform very well with drugs can be difficult to apply to biomedical devices, particularly in early stage assessment and when a new technology radically changes the process of care. This is because there are substantial differences between drugs and other healthcare technologies, as reported in table 1.

Table 1: medical devices versus drug, main differences affecting HTA

Drug	Medical Devices
	Principal action
Pharmaco./Immunologic/Metabolic	Other than principally drugs
Chemical based	Mechanical/Electromagnetic/Materials
	Product life cycle
Long life cycle	Short life cycle
Unchanging compound	Constantly evolving components/parts
	Clinical evaluation
Easy to blind	Difficult to blind (no placebo)
Usually one end users	Multiple end users
Short learning curve	Long learning curve
Less dependent by settings/users	Strongly dependent by settings/users
Easy to standardize for RCT	Complex to standardize for RCT
	Use issues
Efficacy is less user-dependent	User-dependent efficacy
Usually do not require training	Often require intensive training
Complication increase with use	Complication decrease with use
	Diversity
Mainly large multinationals	Mainly small companies/few large co.
Therapeutic	Diagnostic or therapeutic
	Costs
High overheads with quicker return	Varying overheads/slow return
Lower distribution costs	Higher distribution costs
No maintenance/installation	Higher maintenance/installation costs

Electroporation represents an even more complex case study because of its combination of physical effect (i.e. electromagnetic fields alternating the cell membrane permeability to facilitate the transport of drug molecules) and chemical (i.e. the chemotherapeutic drug, in case of electrochemotherapy).

Table 2: Electrochemotherapy peculiarities that may affect its health assessment

Electrochemotherapy
Principal action
High pulsed electric fields
Chemotherapeutic drug
Product life cycle
Years for the electroporator (pulse generators)
Variable for the electrodes
Clinical evaluation
Difficult to blind (no placebo)
Multiple end users
Long learning curve (training performed by the seller)
Strongly dependent by settings/users
Complex to standardize for multicentre RCT
Use issues
User-dependent efficacy
Often require training
Complication decrease with use
It is not possible to predict the effectiveness during treatment
No technology to provide feedback to the therapist during the treatment (i.e. right position of the electrodes, right dosage of EMF)
Peculiarities
Produced by small/medium companies
Mainly used for terminal patients and epidermal applications
Based on a technology (electroporation) that is widely used in other fields (i.e. food industry)
Costs
Not uniform DRG across Europe (in some countries not reimbursed)
Significant distribution/maintenance costs (with respect to drugs)

This case becomes even more challenging when electroporation is applied as minimally invasive treatment, which are rapidly becoming the gold standard for many clinical applications, including oncological applications. In fact, in case of minimally invasive applications the design and the set-up of the medical devices become even more critical for the limited access that the clinicians have to the physiological part that has to be treated. This affects the effectiveness of the treatment, the risks for the patients (i.e. overtreatments) and the costs for the treatment.
Table 2 reports on the main peculiarity of electroporation and particularly of electrochemotherapy, which affects the HTA of this technology.
Although guidelines[1] and HTA reports[2] for Electrochemotherapy of skin tumors have been published in the past years, much less has been done for treatment of deep-seated tumors. Particularly, considering the clinical data available from recent clinical trials, we agreed that liver cancers and bone cancers would be suitable case studies for the definition of a more general pHTA model, which could be used then for other applications.

According to the recent literature, we identified as possible model for the pre-market cost-effectiveness assessment a 4 stages Markov model[3] [1]. This method was chosen also for the availability of free software tools[4] for its implementation.

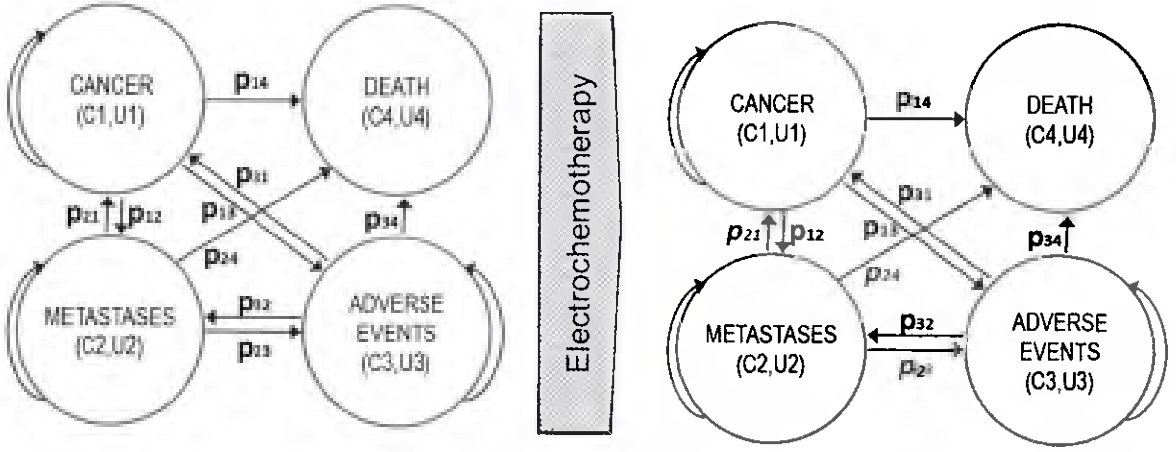

Figure 1: 4 state Markov model for Electrochemotherapy

The hypotesys behind this model is that electrochemiotherapy can affect the transaction probabilities as following:

- Increase the probability of complete metastases removal (p_{21})
- Reduce the probability of adverse events (p_{23})
- Reduce the probability of death in the short term (p_{24})

Therefore, information regarding the % of patient moving from one state to another is required. In order to initialize this model and to run it in different patient populations, several information are required, including:

1. Information describing the population at the baseline (i.e. mean age, BMI, anatomical part of the tumor, staging of the tumor, extension etc)

[1] Australia and New Zealand Horizon Scanning Network (ANZHSN) Report on Electrochemotherapy: https://www.nice.org.uk/guidance/gid-ip1041/documents/electrochemotherapy-for-metastases-in-the-skin-of-nonskin-origin-and-melanoma-overview2

[2] NICE Guidelines, Interventional procedure overview of electrochemotherapy for melanoma metastases in the skin:http://www.horizonscanning.gov.au/internet/horizon/publishing.nsf/Content/6B81AEB3E7EE0001CA2575AD0080F344/$File/Feb%20Vol%2015%20No%205%20-%20Electrochemotherapy.pdf

[3] M. P. M. Craven, S. M., "Early Stage Economic Evaluation with a Small Medical Device Start-up Company using a Markov Model," Journal of Medical Devices, vol. 5, 2011.

[4] Markov Model for pHTA: http://www.nottingham.ac.uk/match/research/tools/markovtoolmain.html

2. Any relevant info about the local team (i.e. number or procedures executed so far, composition of the team...)
3. Info regarding electrochemiotherapy outcomes:
    a. Quality of life (also in the benchmark technology)
    b. Pain assessment
    c. Surgery short term outcomes (i.e. coverage, % of resection rate, mortality, blood loss, surgical time, kind of anesthesia, exacerbations, conversion rate)
4. Info regarding the follow up:
    a. Length of follow-up and frequency of control visits
    b. Clinical outcomes at each wave of the follow-up (i.e. mortality, re-intervention rate, Quality of life...)
5. Any info to quantify costs of the surgery:
    a. Length of the intervention
    b. Consumables
    c. Cost of the device
    d. Training

The same information are required for the benchmark approach, which my change for different kind of tumor. A sensitivity analysis will be performed in order to assess the uncertainty of the estimations achieved with this model. The data for this case study are under collection and the model will be run in the next months.

One of commitments of Dr Pecchia within the COST action is to support the diffusion of HTA methods among partners. With this in mind a seminar on HTA was organized during the STMS visit. The contents of this seminar were similar to the one given in Madrid for the COST Action meeting.

D. Future collaboration with host institution

Future collaborations are foreseen in the field of HTA of medical devices. Although some European project focused on HTA of medical device, few none investigated so far specific methodologies for the pre-market assessment, which could inform the researches during the first stages of researches or development. This is important because by considering the cost-effectiveness and other relevant HTA issues during the R&D of a new methodology allows to make significant changes that will have a big impact on the cost-effectiveness of the related technology when it will be developed.

E. Expected Publications

Once the model will be run, two papers will be prepared: one describing the result and addressed to the community of scientists interested in EMF applications for healthcare (i.e. possible journal BMC Biomedical Engineering online); another describing in details the model employed, addressed to a journal focusing on HTA (i.e. possible journal International Journal of Clinical Engineering and HTA).

Confirmation by the host institution of the successful execution of the STSM:

We confirm that Leandro Pecchia has performed the research work as described above.

Contact Person of Host Institution	Name of researcher
Prof Damijan Miklavčič	Dr Leandro Pecchia
Signature	Signature