University of Ljubljana
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EUROPEAN COOPERATION IN SCIENCE AND TECHNOLOGY

WARWICK
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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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STSM Reference: ECOST-STSM-BM1309-110416-073660

STSM dates: FROM 11th April 2016 TO 16th April 2016

Abstract:

The main goal of the STSM was a determination of need data, for the early cost efficacy analysis of medical electroporation applications, aiming to inform the next steps of research and innovation process. We are planning on build a model for the most established application – electrochemotherapy and on the base of the available results reported in the literature we will simulate the efficiency, also for deep-seated tumors and other applications that just started to evolve. One of the new promising techniques is IRE (irreversible electroporation – "non thermal tissue ablation"), we believe it has a great promise in treating prostate, liver, pancreas, kidney and lung tumors. An additional push with a good cost efficiency analysis would definitely benefit the field. But for a cost efficacy analyses a data about quality of life increase on a year scale are needed, which in our case is a great obstacle. For example IRE is just at the beginning of a stage one clinical trial. Patient treated at this phase are without any other options, they have severe cancer and are not suitable for other already established treatments. For those patients, it is not easy to measure increases of quality of life. Another goal of several oncological emerging applications is to be used on early-diagnosed patients with higher survival options. Quality of life of a patient with severe cancer and bad survival options after the IRE cannot be compared with the one, with better survival options before the procedure. Their quality of life before treatment was not the same, so we can only assume the minimum quality of life increase could be observed from the stage one studies

A. Purpose of the STSM

The purpose of my STSM was getting a clear view of the early cost efficacy analysis. In order to make an appropriate analysis adequate data are needed. Through the STSM I tried to define all the needed data that would enable me to make a cost efficacy analysis for electrochemotherapy and/or IRE.

B. Work Description

I worked in the Laboratory led by Leandro Pecchia. At first I made some exercises to get to know with the Markov model tool and the main principles of HTA. We analyzed the tools functions and discussed how to properly use it for electroporation applications. Afterwards we focused on electroporation and made plans for the future work:

WORK PLAN:

After reviewing how cancer treatment and progression has been modeled using Markov model or decision trees, a 3- or 4-stage Markov model will be developed, depending on the available data. A possible scenario is that the initial state will represent the patients with particular cancer, eventually in different cancer staging. Other states may represent most likely recurrences, metastases, dead, and other disease progresses or treatments responses. For instance, XY in YZ used a N state model as reported in figure (Fig. 1)

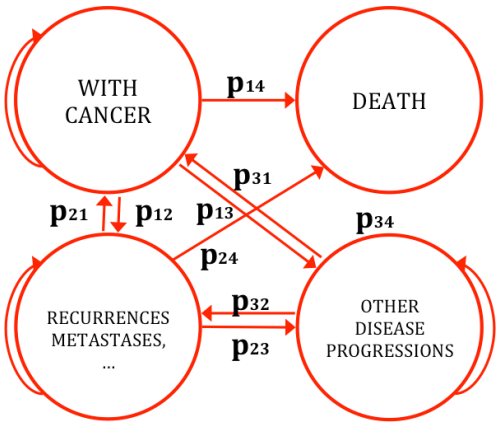

Figure 1: A possible scenario of a four stage Markov Model.

For each state, three information are needed:

1) The probability of transition to all the other states, over 1 year;
2) The cost of staying for 1 year in each state;
3) The utility of patients in each state, expressed in QALY.

The next step will be to model the impact of the technology under investigation on the model developed. For instance, a new technology can change one of the transition probabilities and/or the utility in one or more states and or the cost. In case that information is not available, those data will be estimated using the best possible approached, including:

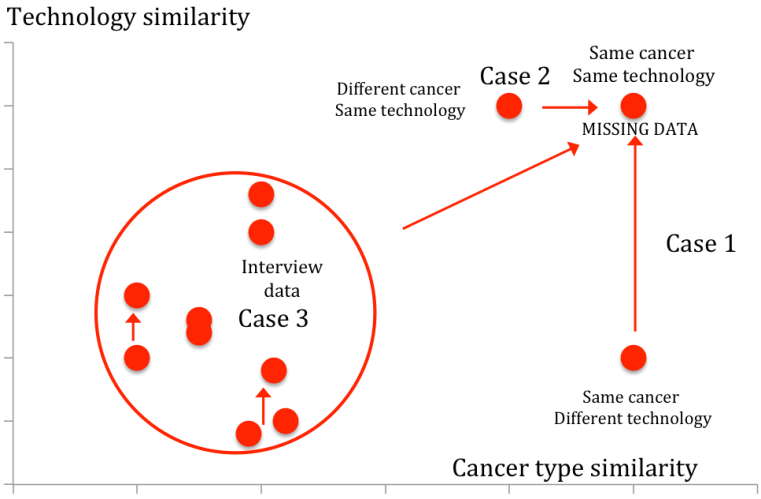

Figure 2: A plot for a better understanding of data collecting and data simulating process.

1) Those data can be adapted from a (more) recent technologies, testing the most possible similar technology in the most possible similar cancer (Fig. 2 : Case 1 and 2). [Fitted with a probabilistic distribution on which we calculate a mean and a standard deviation. Standard deviation will be useful to perform sensitivity analysis later].
2) Alternately, those missing data can be inferred from interview to clinicians (i.e. "Knowing that this is the result [missing parameter] with thermal ablation, what do you think it would be the result with IRE?"]. The answers will be fitted with the best possible statistical distribution, average and standard deviation will be calculated (Fig. 2: Case 3).

Once both cases have been modeled, an incremental analysis will be run, in order to determine the incremental cost-effectiveness ratio and its confidential interval.

Finally, two steps will conclude this study:

1) Perform a sensitivity analysis (the model will be run using a determinist approach but changing the parameter value)
2) Perform a statistical analysis (i.e. using MonteCarlo simulation each subject will move from one state to another according to the given transition probability.)

Regarding the benchmark, there are different opinions. Some tend to compare the innovative technology with the most recent cost-effective technology. Other prefer to compare with the gold standard, in order to make the analysis more replicable.

C. Results

I identified which data are curtail for the analysis and made an extended list of all the needed data. Through the week a tables that need to be fill in for the further work were prepared. I already found some of the missing data.

DATA INCLUDED IN THE MODEL:

Probability of transition between states

We need to collect the response rates for – the electrochemotherapy, IRE treatments and possibly for other technologies (i.e. thermal ablation) in case we need an indirect comparison. We also need to decide if focus on one kind of cancer (possibly with the most possible similar staging) or different kinds aggregated. The techniques under investigation might be more efficient for some specific cancer types then for the others. Or we can make a meta-analysis and find the average values and make only the analysis for treatment not depending on cancer type. A really good cost efficacy result for a specific cancer type would enable easier equipment purchase (electroporator electrode). Resulting in a decrease cost of electroporation for other cancer types, in case the device will not be fully booked for the most cost efficient treatment.

Quality of life evaluation

The reports are missing data about EQ_5D results that should be taken, as specified at clinical trials specifications. The quality of life is reported only as "better", "highly improved", "significantly better",… But for the Markov model analysis a numeric data are required. We will try to get the test results from already finished clinical trials, most likely the EQ_5D tests were done 3 and 8 months after the treatment, so the recalling on a year basis is necessary.

Incremental costs evaluation

Cost evaluation depends on the application. The first necessary cost that must be included is staff (nurses, doctors). In case of deep seeded tumors and in some IRE application, a surgeon is also needed. If IRE is used as minimal invasive ablation technique surgeon does not need to be present, but additional equipment is required (EndoVe - Cork Cancer Research Centre in UCC), allowing the tumor absorbs chemotherapy drugs more efficiently, so less of the chemotherapy drug is used. In case of electrochemotherapy a cost of application of chemotherapeutics Cistplatinum or Bleomycin, intratumoral or intravenous must be considered. The local or general anesthesia is also used.

The second necessary cost is electroporator and electrodes. IGEA (Italy, http://www.igeamedical.com) produced a Cliniporator device, appropriate for electrochemotherapy of smaller cutaneous or subcutaneous tumors and Cliniporator VITAE with higher pulse amplitude that is used for electrochemotherapy of deep seeded tumors or IRE. Cliniporator VITAE is not commercially available and does not have a CE mark yet. In the USA Angyodianmics (USA, http://www.angiodynamics.com) produced NanoKnife, which is used mainly for IRE. For the successful application we need electrodes that may be for single or multiple use. IGEA offers many different electrode types. NanoKnife only has needle electrodes, you can use from one to six per treatment. The amortization cost and annual lease of the device must be also considered.

The cost of a patient stay in the hospital and any other specific treatments that are a result of side effects if any must be also taken into account.

The cost is then calculated per patient. Electroporator and electrode price must be divided with its lifetime and number of patients that we are planning to apply it to on a yearly basis.

If even after all the acquirements the model will still not give a clear result, for a treatment of stage one cancer patients, we will try to find a well-established technique that had the similar cost efficiency at this early stage of evolution. This data will then allow us to simulate the final cost efficacy of electroporation.

All the described data needed to be collected also for comparing technique. Electroporation must be compared to well establish procedure, but that might vary with cancer type, shape, location and size.

TABLES FOR MISSING DATA:

Costs estimations

We need to define a cost of being in each state. Living with cancer is not cheap. I found the attached data (https://costprojections.cancer.gov/annual.costs.html; Mariotto AB et al. 2011) for the USA that might be included in the model. The collected data could present a cost of an initial state. They also made a website with build in model that can simulate a cost per patient trough years for each specific cancer. I think their data could help our calculations (https://costprojections.cancer.gov). Number of people with cancer is increasing with years.

I prepared the following tables that we need to fill in, in order to start with the cost efficacy analysis.

Table 1: For a more clear view and better understanding, I made a table that needs to be filled in, all the missing data are needed for efficient cost effectiveness evaluation.

COST EVALUATION OF ELECTROPORATION	IN MEDICAL APPLICATIONS	PRICE (€)
IGEA	Cliniporator	
	Cliniporator VITAE	
	Electrode 1	
	Electrode 2	
	...	
	Maintenance and amortization	
	Annual lease	
Cork Cancer Research Centre in UCC	EndoVe	
Angiodynamics	NanoKnife	
	One electrode	
	Maintenance and amortization	
	Annual lease	
Staff	Without surgeon	
	With surgeon	
Chemotherapeutic	Cistplatinum intratumoral	
	Cistplatinum intravenous	
	Bleomycin intratumoral	
	Bleomycin intravenous	
Anesthesia	Local	
	General	
Stay in the hospital	Per day	

Cancer (incidence) survival rates and treatments efficacy rates:

Incidence of a specific cancer must be estimated. It will help us determine how many patients per year will/could be treated, when the technique will/would be used also on patients with lower cancer stages and better survival options.

Data and prediction values for USA can be find here: https://costprojections.cancer.gov/graph.phpt

And for the UK here: http://www.cancerresearchuk.org/health-professional/cancer-statistics/risk

From statistic reviews of studies I will try to obtain treatment efficacy rates for all the cancer types treated with IRE and electrochemotherapy. In addition to make an analysis we also need all data for comparable technique that is cancer dependent. I will try to fill in all the data in attached table (Table 3).

The one problem we will be coping with, is also how to convert results from a specific tumor treatment rates to people. Because cost efficacy analysis bases on a number of people treated, our results from low stage trials give us the response rates for a metastases treated and not patients (each patient can have more metastases).

Table 2: Tables for missing data collection.

Cancer type	Incidence/ state 1	ECT			IRE		
		state 2	state 3	state 4	state 2	state 3	state 4

Comparable technique		
state 2	state 3	state 4

Quality of life evaluation:

An article about stage three clinical trial of electrochemotherapy should be published in a week. Results from EQ_5D quaternaries that help us to evaluate quality of life, will also be included. Information about how much the comparable technique improves the quality of life is also required. The average values will be calculated, and if not collected a year after the procedure, they will be reduced on a year scale.

Table 3: Tables for missing data collection of QALY.

Cancer type	ECT	IRE	Comparable technique

D. Future collaboration with host institution

After collecting all the data, a cost efficacy analysis will be done and an article written.

E. Expected Publications

We are planning to write an article, after we obtain expected results.

F. Other Comments

No other comments.

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

We confirm that Eva Pirc has performed the research work as described above.

Leandro Pecchia

Signature

Eva Pirc

Signature