Challenges of Trustable AI and Added-Value on Health
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Personalising Symptoms Reporting in Telemonitoring Applications for Cancer Patients

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Abstract. Patient reported outcomes have been shown to be predictive of cancer patients' prognosis, and their monitoring through electronic applications have been shown to positively impact survival. On the other hand, patient apps in general show a number of criticalities that often lead patients to abandon their use. One of them is usability. A scarce attention to usability during app development leads to unsatisfactory user experience. In this work, we present an algorithm to facilitate patient symptoms reporting, by personalising the list of symptoms according to their probability of occurrence in the specific patient. This avoids searching long lists of items, thus decreasing the patients' burden in symptom reporting.

Keywords. Patient reported outcomes, cancer, interface terminology, telemedicine, personalised medicine.

1. Introduction

There is increasing evidence on the benefits of telemonitoring systems that allow cancer home patients to report adverse events during oncological treatments [1][2][3]. Some of them [4] start being approved as "digital therapeutics" by regulatory organisations such as FDA. Using those systems, patients can enter symptoms as soon as they appear, and this represents two advantages. First, reporting is more accurate, because the system may ask patients to enter details that could be forgotten if asked by the physician at the next visit, and second, doctors can see what's happening in-between control visits. In fact, type, severity, and duration of symptoms are essential for both doctors and decision support algorithms, for a correct interpretation and management of adverse drug events (ADE). Thus, telemonitoring apps should offer any possible facility to maximize the patient's compliance with accurate symptom reporting. Moreover, while reporting could be clear and precise even using free text, using structured data is advisable, to allow easier and faster electronic data elaboration. Therefore, first of all, an interface terminology must be chosen, including all the possible symptoms a patient could experience, which is a very high number, and then users must be provided with facilities for quickly searching the symptom(s) to be entered. To make some examples, the symptom list can be shown as a flat list in alphabetical order, or symptoms can be

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grouped according to the body district affected or to the physiological system involved, or patients could start writing a text and the *autocomplete* function looks for the possible compatible labels, etc. In any case, even after those filters, the number of remaining symptoms, among which the patient should choose, could be uncomfortably high. Since there is evidence that ADEs frequency depends on cancer type, treatment, and treatment duration, in this paper we present an algorithm for sorting those remaining symptoms according to their probability of occurrence, for *that* patient at *that* time, in order to maximize the chance for a patient to find the symptom among the top ones in the list. This will improve the user experience with the app, thus increasing the chance of using it over a long period. The paper describes also the data model the algorithm runs on top of, which stores information collected from both the patient's profile and from the literature. Since this work is part of a European project, the next section will briefly illustrate the project objectives.

2. The CAPABLE project

CAPABLE is a EU Horizon2020 project (Jan 2020-Dec 2023), currently in the middle of its development, which implements an overall intervention strategy for improving cancer patients' wellbeing, both physical and mental. It helps increase patients' awareness about their condition, understand and cope with daily needs, become more proactive and more positive in their cancer journey. To this purpose, patients will be provided with a smartwatch (for the automatic acquisition of physical activity and some vital parameters), and an app for reporting symptoms and answering some follow-up questionnaires. The app will also send recommendations to patients, based on scientific evidence and/or approved by the CAPABLE experts panel, and suggest some exercises, both physical and mental, to achieve objectives that patients, at the enrollment, may have set together with their oncologist. CAPABLE targets also the multidisciplinary healthcare team who takes care of patients, namely oncologists, psychologists and nutritionists. Doctors will rely on a web interface that will visualise their home patients' data and will suggest evidence-based interventions for preventing and managing adverse events. Since this paper deals with symptoms reporting, the next section will describe this functionality in more detail.

For structured symptom reporting, the project relies on the Common Terminology Criteria for Adverse Events (CTCAE), developed by NIH, nowadays used at an international level to represent ADEs. More precisely, we use a subset of 130 terms, obtained by excluding those events that cannot be noticed by patients or their caregivers (for example toxicities that can be detected only by diagnostic laboratory tests) or that are not of interest for cancer patients, according to medical experts' opinion. To further filter the symptoms at runtime, a body-shaped graphical interface allows indicating the body part affected, for example choosing the head will filter out all symptoms related only to limbs or torax. Finally, the autocomplete function is available. These functionalities, present also in other applications [5], are useful to shorten the symptom list that a patient has to examine on his small smartphone interface, for selecting the specific symptom he wants to enter. However, they do not take into account that symptom incidence varies according to cancer, treatments and time. In the following, we show how we exploited literature data about ADE incidence to build an algorithm that considers also those aspects, and that delivers a final, dynamic and patient-specific symptom list, which is more likely to visualize the most probable ADEs at the top.

3. Evidence about Adverse Events of Oncological Treatments

The literature offers several data about the overall incidence of ADEs that occur for specific cancer patients undergoing specific treatments. For our proof of concept, we limited our search to the treatments currently used according to the ESMO clinical guidelines (www.esmo.org/guidelines) for melanoma and renal cell cancer, which are the two main pathologies considered in CAPABLE. We relied on phase III clinical trials, being meant (also) to assess the risk profile of the drugs on large samples, thus putting particular attention to the ADE occurrence [6][7][8][9][10]. For several ADE types, in addition to overall incidence, we found interesting information about time courses [6][11][12]. As an example, Figure 1 shows the time-related onset probability of some ADEs caused by immunotherapy with nivolumab. It can be noticed that: (a) ADEs appear in different times; (b) the first weeks are the most affected; (c) some ADEs are more frequent in the early treatment phase but can also occur very later.

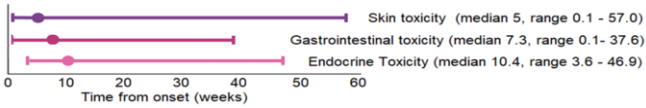

Figure 1. Onset time (median and range) for different ADEs caused by nivolumab - Adapted from [6]

Similar information can be found for ADEs related to other active principles. In addition to incidence, it's important to estimate the event duration: as a matter of fact, recovery time may last from a few days to months [6].

4. Methods

We used literature derived data such as the ones shown in Figure 1, to simulate patterns of time variant incidence for each ADE considered. We have chosen the lognormal distribution, since it is defined on a positive values domain, it may account for outliers (in our case very late ADEs), and its two parameters μ and σ allow us to shape the peak position and kurtosis appropriately. Thus, this distribution family is suitable to represent asymmetrical distributions, with the peak on the left and different time spans. Figure 2 (left) shows the Matlab code allowing to assess a specific distribution (namely the skin toxicity), while in the right the simulated distributions are shown for the considered ADEs, using *week* as a suitable time granularity.

```
%% skin

% interval on which the pdf of the lognormal distribution is evaluated
x = 0:0.1:60;
t0 = 1;
t1 = 60;

% mu coefficient, equal to the natural logarithm of the median
mu_skin = log(6.1);

% sigma coefficient
sigma_skin = 0.8;

% pdf evaluation in the interval x
y_skin = lognpdf(x,mu_skin,sigma_skin);

% pdf plot
figure('name','pdf - skin')
plot(x,y_skin)

% pdf explicit expression
f = @(y) 1./(sigma_skin.*y*sqrt(2*pi)) ...
    .* exp(-(log(y)-mu_skin).^2/(2*sigma_skin^2));
% weekly coefficients vector
w_skin = zeros(60,1);

% weekly coefficients evaluation as the probability that ADEs
% of the skin category occur during week t
for t = t0:t1
    w_skin(t) = integral(f,t-1,t);
end
```

$$f(x) = \frac{1}{x\sigma\sqrt{2\pi}} e^{\left(-\frac{(\ln(x)-\mu)^2}{2\sigma^2}\right)}$$

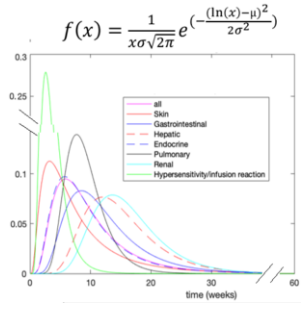

Figure 2. (Left) Matlab code used to approximate onset time distribution of a specific ADE category, and (right) the lognormal distribution formula and the obtained distribution models

In particular, the *for* cycle in the bottom of the Matlab code fills in the array w_skin with the integral of the probability density calculated within each week from the therapy start. Those values are a sort of "weekly coefficients", representing the probability that an ADE occurs within each week (for sake of demonstration we limited the time horizon to 60 weeks), under the hypothesis that total probability is 1. However, since each ADE probability is less than one, those coefficients are multiplied by the actual overall probability of occurrence found in the literature as described in the above section.
Both data gathered from the literature and the calculated weekly coefficients have been structured into a relational database (DB), illustrated in Figure 2 through its entity-relationship (ER) diagram. The publications that have been consulted to retrieve data from clinical studies are listed in the *Paper* entity through their DOI. *Cohort* represents the cohorts that have been studied in the selected papers. Each cohort is defined by a *CohortType*, which is a combination of type of cancer and therapy. In some rows the therapy does not correspond to a specific treatment (e.g. Nivolumab monotherapy, Nivolumab plus Ipilimumab) but is set as "pooled". In this case the CohortType is a dummy, since its only purpose is to gather from the database the weekly coefficients for a pool of treatments when the coefficients for a particular cancer-therapy pairing are not available; this procedure only works when the treatment is included in the *TreatmentPool* for that cohort type (i.e., if the DB contains weekly coefficients for a pool of treatments including drug A and the combination of drugs A and B, those coefficients will not be used for drug C). *AdverseEvent* contains the list of ADEs, whose frequency of occurrence in each cohort is stored in *Frequency*. The entity *Category* contains the categories to which the adverse events belong. This is important to link adverse events to weekly coefficients, that have been calculated for ADEs categories, and are contained in *Coefficient*.

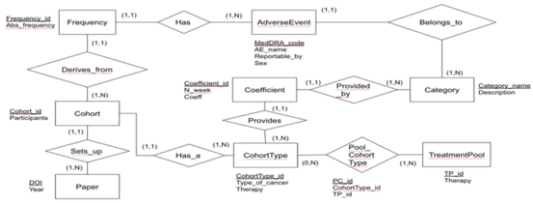

Figure 3. ERdiagram of the database used for storing literature data about ADE incidence

This DB is exploited by the symptom prioritization query described in the next section.

5. Results

To demonstrate the potentiality of the algorithm, we developed a lite Matlab interface, which allows entering the variables that affect ADE incidence, including the treatment type and its start date (Figure 3 left). A set of SQL queries is then run on the DB, and both overall and dynamic frequency (OF and DF) of the symptoms are generated. Figure 3 (right) shows the results of the algorithm when run for weeks 3 and 10 from Start Date. The OF values account for the incidence over the full treatment period, while DF also for the time distribution, thus referring to the single actual week considered. In the figure, we sorted the symptom list according to DF. The ordering that would have been generated considering OF is remarkably different. In our example, a melanoma patient treated with Nivolumab, Fatigue is overall the most frequent ADE, but if we take into

account time distribution, this is true only after certain time (week 10 in our example), while in week 3 other symptoms like maculo-papular rash are more likely to arise.

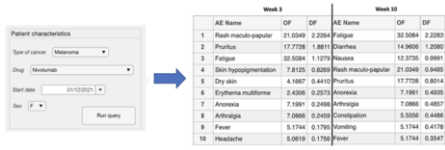

Figure 4. The different ordering of ADEs when considering the time-variant incidence. OF = Overall Frequency; DF = Dynamic Frequency

6. Discussion and Conclusions

This paper is a proof of concept (PoC) of how personalized medicine can be implemented in a digital therapeutics. We proposed an interface terminology that varies over time according to the probability of ADE occurrence, in order to improve the user experience with the app. As a PoC, our study has some limitations. The whole ADE list accounts for 130 items, but we did not collect time-variant data for all of them. On the other hand, the papers considered in this work deal with the most frequent ADEs, so we think that results can provide a good idea of the real-world effectiveness of our algorithm.

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