Feasibility Estimation for Clinical Trials

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Abstract: At least 90% of clinical trials are extended by at least 6 weeks because investigators fail to enroll patients on schedule (Ledford, 2011). It is therefore important at trial design-time to have good insight in how the choice of the eligibility criteria affects the recruitment rate. Based on that insight, trial designers can then adjust the eligibility criteria in order to ensure realistic recruiting rates. In this paper we propose a simple mathematical model to determine how eligibility criteria determine the recruitment rate. Our model allows us to calculate a newly proposed "relative" measure for the effect of an eligibility condition on the recruitment rate: instead of estimating the recruitment rate of the total set of conditions, our new relative measure calculates the effect of adding, removing or changing an individual condition in the light of the other conditions. This allows for a much more fine-grained insight into the effect of individual trial-conditions, and into the interactions between the conditions. We have implemented this mathematical model in efficient algorithms, and we demonstrate our model on both real and synthetic patient data. Our experiments show that almost all medical trials in our test corpus contain logically redundant criteria, and that this redundancy can only be revealed with our new relative feasibility measure (and not with the classical absolute feasibility measure). To increase the reproducibility of our results, we have made our datasets available online.

1 INTRODUCTION

Motivation. Trial recruitment is challenging for medical researchers, who frequently overestimate the pool of qualified, willing participants (Galbreath et al., 2008). A recent Nature paper reported that at least 90% of trials are extended by at least 6 weeks because investigators fail to enroll patients on schedule (Ledford, 2011). But already over a decade ago, recruitment challenges were reported to be the cause of 45% of study delays, with delays often exceeding six months(Anderson, 2001), while another meta-study at the time reported that 17% of trials studied failed to reach even half their target recruitment (Haidich and Ioannidis, 2001). These problems persist until the present day: a recent report prepared for the UK Parliament reports that of 114 trials studied, less than one-third recruited their original target within the time originally specified, and around one-third had extensions (Campbell et al., 2007). The same report also succinctly describes the problems caused by inadequate recruiting rates: "One of the most commonly reported problems with the conduct of multicentre RCTs, however, is that recruitment is slower or more difficult than expected, with many trials failing to reach their planned sample size within the timescale and funding originally envisaged (Gates et al., 2009). If the target sample size is not achieved, the trial has less statistical power to detect potentially important clinical differences between the groups, so the results may be less useful. In addition, if recruitment has to be extended to reach the required sample size, the trial will cost more and take longer, delaying the use of the results in clinical practice".

Research Question. Given these persistent and costly problems, it is clearly important that trial designers are given the tools to perform an accurate estimate of *trial feasibility* (Wang and Bakhai, 2006) including accurate estimates of recruiting rates. Such tools will help them to avoid overly restrictive trial criteria, thereby avoiding low recruitment rates.

This leads us to the central question of this paper: *given the characteristics of the patient population, which trial conditions will lead to which cohort size?*

Scope. A general notion of trial feasibility would consider all relevant issues which may have effect on the feasibility of a trial. These include issues such as availability of medical equipment, costs, legal and regulatory conditions, skills and availability of staff, and many others (Rajadhyaksha, 2010). Such considerations are out of scope of the current paper, where

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we focus exclusively on the estimation of recruitment rates induced by the eligibility criteria of a clinical trial, given properties of the cohort population.

Trial feasibility estimation is closely related to the well-studied task of trial recruitment. Both feasibility estimation and recruitment rely on answering the same question: does a set of trial conditions apply to a given patient? Nevertheless, there are important differences, which make trial feasibility estimation substantially different from trial recruiting: patient recruitment considers how to apply a criterion to a patient, whereas trial feasibility estimation investigates the effects of applying a criterion to a patient for recruitment rates. In recruitment, the trial criteria are fixed, and the patient population changes as new patients arrive, while in feasibility estimation the (properties of the) patient population are fixed, and the trial criteria can be varied in order to obtain the desired recruitment rate. Finally, trial recruiting is considered to be "on-line", i.e., is executed in a clinical setting, while trial feasibility is considered to be "off-line", i.e., is executing during the design phase of a trial.

Approach. In this paper, we will distinguish two kinds of trial feasibility: absolute feasibility and relative feasibility. The former considers the effect of a total set of conditions, whereas the latter considers the effect of adding, removing or changing individual conditions in the presence of other conditions. In this paper, we propose a simple mathematical model of trial feasibility to explore the distinction between absolute feasibility and relative feasibility. This will show that our novel notion of relative feasibility is a useful notion in the design of a clinical trial.

A workflow of trial feasibility usually consists of the following steps:

1. Start with new or existing trial design
2. Determine required cohort size (statistical power)
3. Determine absolute feasibility of current design
4. Explore relative impact of modifying some conditions
5. Repeat steps 3-4.

This workflow has been implemented and integrated with SemanticCT, a semantically-enabled system for clinical trials (Huang et al., 2013b; Huang et al., 2013a). We have conducted several experiments to test our approach to trial feasibility analysis with a set of real patient data at a clinic in the Netherlands, and with a set of synthetic patient data, which are generated by using a knowledge-based patient data generator (Huang et al., 2013c). These experiments show that the notion of relative feasibility is indeed very useful for the analysis of trial feasibility.

Structure and Contributions of this Paper. The rest of this paper is organized as follows: Section 2 gives a brief overview of the relatively small literature devoted to trial feasibility analysis. Section 3 presents a formal model of trial feasibility. Section 4 discusses the implementation of trial feasibility. Section 5 reports several experiments and make the evaluation on the proposed approach. Section 6 discusses the findings from our experiments, and the last Section 7 concludes and briefly discusses future work.

2 RELATED WORK

(Weng et al., 2010) is an excellent review of formalization of eligibility criteria. Often the formalization of eligibility criteria is done for purposes of trial recruitment, or for authoring criteria. In our work we focus on the task of trial feasibility estimation, which of course also needs a formalised version of criteria in order to test eligibility statistics across a cohort. We use a rule-based formalization for the eligibility criteria (Huang et al., 2013a).

EligWriter (Gennari et al., 2001) and Design-a-Trial (Nammuni et al., 2004) support the reuse of eligibility criteria when authoring clinical trials, while ERGO (Tu et al., 2009) supports the annotation of such criteria during authoring. The system Design-a-trial (Nammuni et al., 2004) helps to determine various statistical values that are needed for trial design (for instance minimal number of participants), as well as ethical issues (e.g. choosing a drug with the least side effects) and preparing required documentation, but it does not provide any support for trial feasibility or design of eligibility criteria.

Epoch (Shankar et al., 2006) is a tool to support clinical trials management. The increasing complexity of clinical trials has generated an enormous requirements for knowledge and information specification at all stages of the trials, including planning, documentation, implementation, and analysis, justifying the need for such a tool.

In (Thew et al., 2011), the authors have developed FARSITE (Feasibility Assessment and Recruitment System for Improving Trial Efficiency), a system to support the evaluation of trial feasibility by providing accurate assessments of the number of patients eligible for a particular trial. FARSITE also provides support for automated patient recruitment. FARSITE runs recruitment criteria for on-going clinical trials and compares the estimated number of eligible patients for the trial with actual recruitment rates. A strong correlation is observed between protocols with a low FARSITE recruitment estimation and trials struggling to recruit participants.

Other tools that enable users to define the eligibility criteria and return counts for patients that match the criteria definitions are i2b2/SHRINE (We-

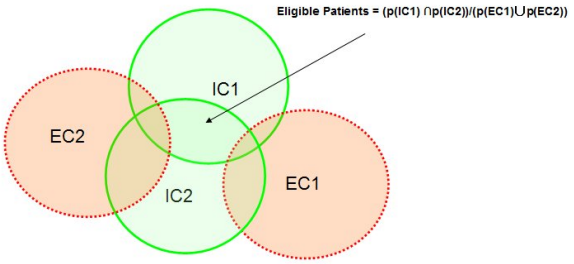


Figure 1: Trial feasibility with two inclusion criteria and two exclusion criteria.

ber et al., 2009) and VISAGE (Zhang et al., 2010). However none of these systems has any notion of absolute feasibility or relative feasibility, such as those that we will introduce in this paper.

Qiagram[1] is a data exploration tool, designed to make data more useful through visualisation of data-queries. When applied to medical trials, Qiagram provides a visualisation of the inclusion and exclusion criteria as complex queries. Again, there is no analysis of the inclusion and exclusion criteria in depth by using notion as absolute and relative feasibility.

From this brief survey, we therefore conclude that, to the best of our knowledge, no notions of relative feasibility has been defined in the literature, nor has any such notion been effectively implemented.

3 A FORMAL MODEL OF TRIAL FEASIBILITY

In this section, we propose a light-weight formal model of trial feasibility. We consider a set of patients P, and a set of criteria C, which is the union of two disjoint sets: the inclusion criteria IC, and the exclusion criteria EC. The function p is a mapping from the criteria C into a subset of P, which states those patients meet the condition. Formally, $p : C \rightarrow Powerset(P)$ and $p(c) \subseteq P$ for each $c \in C$. We use the notation $ep(IC, EC)$ to denote the set of eligible patients with respect to the inclusion criteria IC and the exclusion criteria EC.

If we consider two inclusion criteria ic_1 and ic_2, and two exclusion criteria ec_1 and ec_2, the eligible patients are those that simultaneously meet both inclusion criteria and do not meet any exclusion criterion. This can be formalized as

$$ep(\{ic_1, ic_2\}, \{ec_1, ec_2\}) = (p(ic_1) \cap p(ic_2)) \setminus (p(ec_1) \cup p(ec_2)).$$

which is shown in Figure 1.

[1]http://www.slideshare.net/shc66columbia/clinical-trial-feasibility-using-healthcare-data

In general, for the inclusion criteria IC and the exclusion criteria EC, the eligible patients are those patients meet all the inclusion and none of the exclusion criteria. It can be formalized as:

Definition 1 (Eligible Patients)**.**

$$ep(IC, EC) = \bigcap_{i \in IC} p(i) \setminus \bigcup_{e \in EC} p(e).$$

Thus, the absolute feasibility of a criterion $AF(c)$ is defined to be the percentage of patients that would be eligible out of the total patient set. Thus, for an inclusion criterion c, the absolute feasibility is the ratio of eligible patients $p(c)$ to the total patient set, i.e., the patient set P. Similarly, for an exclusion criteria, $p(c)$ denotes that the set of the patients meet the criterion c. Thus, the eligible patients would be the set $P - p(c)$. Formally:

Definition 2 (Absolute Feasibility)**.**

$$AF(c) = |p(c)|/|P| \quad for\ c \in IC.$$
$$AF(c) = 1 - |p(c)|/|P| \ for\ c \in EC.$$

If the set of criteria C is an empty set, all patients should be considered to be eligible. If $p(c)$ is an empty set, that means that no patients are eligible for criterion c. In that case, the criterion c is said to be an unsatisfiable criterion (with respect to the patient set P). We have the following formal propositions about the absolute feasibility:

Proposition 1.
(1) If an inclusion criterion c is unsatisfiable, then its absolute feasibility is 0, i.e., $AF(c) = 0$.
(2) If an exclusion criterion e is unsatisfiable, then its absolute feasibility is 1, i.e., $AF(e) = 1$.

The absolute feasibility of a criterion tells us about the recruitment rate when the criterion is considered in isolation. However, we are interested in the effect of a single criterion with respect to other criteria. To make this clear, consider the following two observations.

Observation 1. *A bigger coverage of exclusion criteria does not necessarily lead to a lower feasibility.*

That observation can be seen in Figure 2, in which a bigger exclusion criterion $EC3$ has no intersection with the intersection of the two inclusion criterion $IC1$ and $IC2$. Thus, $EC3$ does not lead to any change in the eligible patient set.
Similarly:

Observation 2. *A bigger coverage of inclusion criteria does not necessarily lead to a higher feasibility.*

That observation can be seen in Figure 3, in which a bigger inclusion criterion $IC3$ already covers the intersection of the other two inclusion criteria $IC1$ and

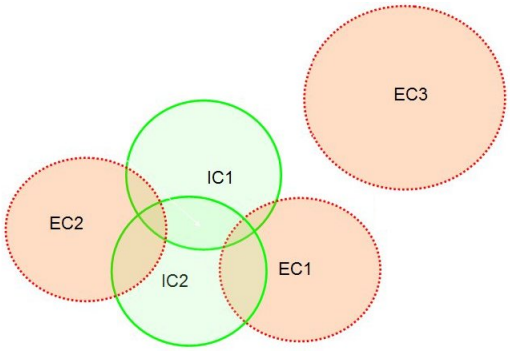


Figure 2: Observation 1.

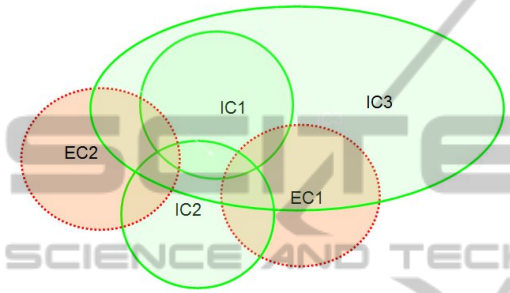


Figure 3: Observation 2.

$IC2$. Thus, $IC3$ does not lead to any change in the eligible patient set. This shows that the interaction between inclusion/exclusion criteria play a crucial role.

We therefore propose the *relative feasibility* which compares the differences with and without a criterion in the light of all the other criteria. Consider a case which is shown in Figure 4. Here, the relative feasibility RF of the inclusion criterion $IC1$ is the ratio of the cardinality of the set a to the cardinality of the union set of a and b. Similarly, the relative feasibility of the exclusion criteria $EC1$ is the ratio of the cardinality of the set a to the cardinality of the union of the set a and the set d. Namely,

$$RF(IC,EC,IC1) = |a|/|(a+b)|, \text{ for } IC1 \in IC,$$
$$RF(IC,EC,EC1) = |d|/|(a+d)|, \text{ for } EC1 \in EC.$$

As we have discussed above, the eligible patient function $ep(IC,EC)$ is defined as:

$$ep(IC,EC) =_{df} \bigcap_{i \in IC} p(i) \setminus \bigcup_{e \in EC} p(e).$$

We will now use the notation $ep(IC,EC,c)$ to denote the eligible patient set if the criterion c is not considered. Formally:

Definition 3 (Eligible patients without criterion c)**.**

$$ep(IC,EC,c) =_{df} ep(IC \setminus \{c\}, EC \setminus \{c\}).$$

Thus, we have:

$$ep(IC,EC,c) = \bigcap_{i \in IC \setminus \{c\}} p(i) \setminus \bigcup_{e \in EC \setminus \{c\}} p(e).$$

It is easy to prove the following proposition:

Proposition 2. *Removing a criteria never makes the eligible patient set smaller (and possibly larger):*

$$ep(IC,EC) \subseteq ep(IC,EC,c) \text{ for any } c \in IC \cup EC.$$

We define the relative feasibility RF for a criterion c as follows:

Definition 4 (Relative Feasibility)**.**

$$RF(IC,EC,c) = \begin{cases} \text{if } c \in IC: \\ \dfrac{|ep(IC,EC)|}{|ep(IC,EC,c)|} \\ \\ \text{if } c \in EC: \\ \dfrac{|(ep(IC,EC,c) \setminus ep(IC,EC))|}{|ep(IC,EC,c)|} \end{cases}$$

$RF(IC,EC,c)$ is defined as 0 when $ep(IC,EC,c) = \emptyset$.

Assume that a trial-designer is removing a criterion c to get from an existing (small) population to a new (larger) recruited population, then $ep(IC,EC)$ is the "old" population, $ep(IC,EC,c)$ is the "new" population, and $ep(IC,EC,c) - ep(IC,EC)$ is the "gain" in population by removing c. The definition above can then be intuitively read as: for an inclusion criteria c, $RF(IC,EC,c) = old/new$, and for an exclusion criteria, $RF(IC,EC,c) = (new-old)/new = gain/new$.

The interpretation of $RF(IC,EC,c)$ is very different for inclusion and exclusion criteria: for inclusion criteria, the meaning of RF is the fraction of the new population that was already in the old population. Thus, if we aim to increase the population, we should remove a c that has a small value of RF. For exclusion criteria, the meaning of RF is the fraction of the new population that was gained over the old population. Thus, if we aim to increase the population, we should aim to remove a c that has a large value of RF. So, sometimes we must minimise RF to get a larger population (inclusion) and sometimes we must maximise RF to get a larger population (exclusion).

In order to emphasise the asymmetry in the definition above, we can introduce two new notations for relative feasibility RF as follows:

$$RF_i(IC,c) = \frac{|ep(IC,EC)|}{|ep(IC,EC,c)|}$$

for $c \in IC$, and

$$RF_e(EC,c) = \frac{|ep(IC,EC,c) \setminus ep(IC,EC)|}{|ep(IC,EC,c)|}$$

for $c \in EC$.

It is easy to see that the following propositions hold, which are useful to tell us about the relative feasibility and its relation with the absolute feasibility.

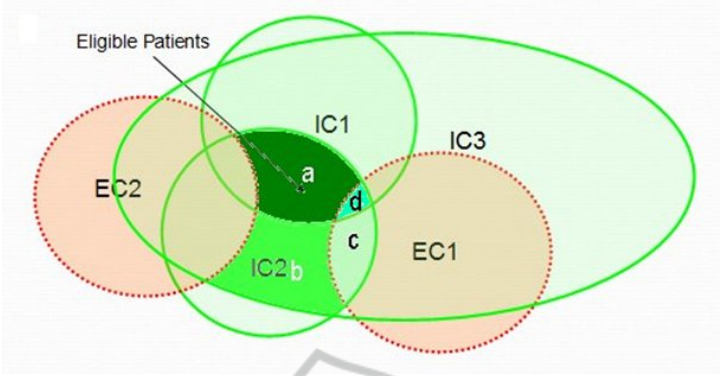


Figure 4: Relative Feasibility.

Proposition 3.
1. (Unsatisfiability) If c is unsatisfiable and $c \in IC$, then $ep(IC,EC) = \emptyset$.
2. (Zero inclusion feasibility) If c is unsatisfiable and $c \in IC$, then $RF_i(IC,c') = 0$ for $c' \in IC$.
3. (Inclusion Singleton) $RF(\{c\},\emptyset,c) = AF(c)$ for any c.
4. (Exclusion Singleton) $RF(\emptyset,\{c\},c) = 1 - AF(c)$ for any c.

A criterion c is said to be implied by other criteria if $ep(IC,EC) = ep(IC,EC,c)$. This means that removing an implied criterion will not lead to any change on the feasibility (ie. the same population). Thus, we have the following propositions:

Proposition 4.
1. (Implied Inclusion Criteria) For any $c \in IC$, if c is implied by other criteria, then $RF(c) = 1$.
2. (Implied Exclusion Criteria) For any $c \in EC$, if c is implied by other criteria, then $RF(c) = 0$.

The proposition above tells us that we should focus on those inclusion criteria for which the relative feasibilities are not equal to 1 and those exclusion criteria for which the relative feasibilities are not equal to 0, if we want to increase the feasibility of a clinical trial. Remember $RF_i(c)$ means the fraction of the new population (=without c) that was already in the old population (=with c). $RF_e(c)$ means the fraction of the new population (=without c) that was gained over the old population (=with c). A satisfiable inclusion criterion c is said to be inconsistent with other criteria if $ep(IC,EC,c) \neq \emptyset$ and $ep(IC,EC) = \emptyset$.

Proposition 5.
1. (Inconsistent Inclusion Criteria) For any $c \in IC$, if c is inconsistent with other criteria, then $RF_i(IC,c) = 0$.
2. (Inconsistent Exclusion Criteria) For any $c \in EC$, if c is inconsistent with other criteria, then $RF_e(EC,c) = 0$.

The proposition above tells us that we should avoid those inconsistent criteria. Namely, removing those inclusion criteria for which the relative feasibilities are equal to 0 and those exclusion criteria for which the relative feasibilities are equal to 1. We discuss those cases in the section about the experiments of trial feasibility.

4 IMPLEMENTATION

We have implemented the proposed approach of trial feasibility in SemanticCT[2], a semantically-enabled system for clinical trials (Huang et al., 2013b; Huang et al., 2013a). The goal of SemanticCT is not only to achieve interoperability by semantic integration of heterogeneous data in clinical trials, but also to facilitate automatic reasoning and data processing services for decision support systems in various settings of clinical trials.

In SemanticCT, the trial feasibility service provides functionality to change eligibility criteria and their parameters, and to support this process by calculating the absolute and relative feasibility (Figure 5). The following different parameters are taken into account in this process:

- Cohort Size: the number of patients required for running the trial. This is typically determined as the result of an analysis about the desired statistical power of the trial.
- Consent Rate: The percentage of patients that will agree to take part in the trial. This is typically determined on the basis of experience in other trials at the same location, or of similar trials in other locations.
- Dropout Rate: The percentage of patients that is likely to stop participating during the trial. Again, this number is typically determined by previous experience and statistics.

[2]http://wasp.cs.vu.nl/sct

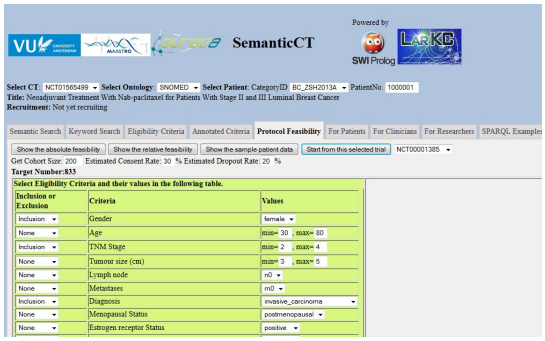


Figure 5: GUI of Trial Feasibility.

- Target Number: The number of patients that should be approached, in order to meet the cohort size, given consent rate and dropout rate.

$$TargetNr = \frac{CohortSize}{ConsentRate * (1 - DropoutRate)}$$

The user can select an initial set of trial eligibility criteria either from scratch or by using a trial template. Figure 5 shows an example which uses a previously defined trial NCT00001385[3]. The user can also select different parameters for the cohort size, the consent rate and the dropout rate. Typically, sophisticated statistical techniques are used to determine these, and in this paper, we assume that these are determined by other services. The designers of a clinical trial can then follow the workflow described in the previous section to find a balance between medical specificity of the eligibility conditions and the trial feasibility.

5 EXPERIMENTS

In this section, we present a set of experiments to test the value of our trial feasibility measures. For this experiment, we provide a set of clinical trials for breast cancer from the NCI corpus of clinical trials[4] as well as a clinical trial for breast cancer at the Dutch clinic MAASTRO[5]. In combination with these two trials, we use two sets of patients data for our experiments. The first data set *ZSH*2013*A* is artificial data of 10,000 breast cancer patients, which are generated with a knowledge-based patient data generator (Huang et al., 2013c). This generates patient data that are artificial, but that are guaranteed to follow statistically realistic distributions of values, using rules that are based on background knowledge from the medical literature. The second data set *MST*2013*A* is real data of 3,312 breast cancer patients at the MAASTRO clinic.

Using these data, we performed 16 experiments of calculating trial feasibility with different criteria, different parameters in those criteria, and different cohort sizes. To simplify the description of the experiments, we assume that those experiments use the same consent rate (30%) and the same dropout rate (20%). Of course, it is quite easy to use different consent and dropout rates for different experiments. To increase the reproducibility of our results, we have made available both the full set of trials and our synthetic patient-data[6] as well as the anonymised patient data from the MAASTRO clinic[7].

The results of the 16 experiments on trial feasibility are shown in Table 1. In the table, we use the sign $\Rightarrow$ to denote that a criterion is modified into another criterion. For example, $stage(2,4) \Rightarrow stage(1,4)$ means that the criterion 'tumor stage from 2 to 4' is modified into the criterion 'stage from 1 to 4'. We use the sign '-' to denote that a criterion is removed. For example, menopausal(premenopausal)- means that the criterion 'menopausal status is premenopausal' is removed. Similarly, we use the sign '+' to denote that a criterion is added.

For example, in the experiment no.1, we select the trial NCT00001385 as the template, with a cohort size of 200, a consent rate of 30% and a dropout rate of 20%, leading to the target number 833, according to the equation above. The three inclusion criteria and three exclusion criteria from experiment no. 1 are described in Figure 6(a).

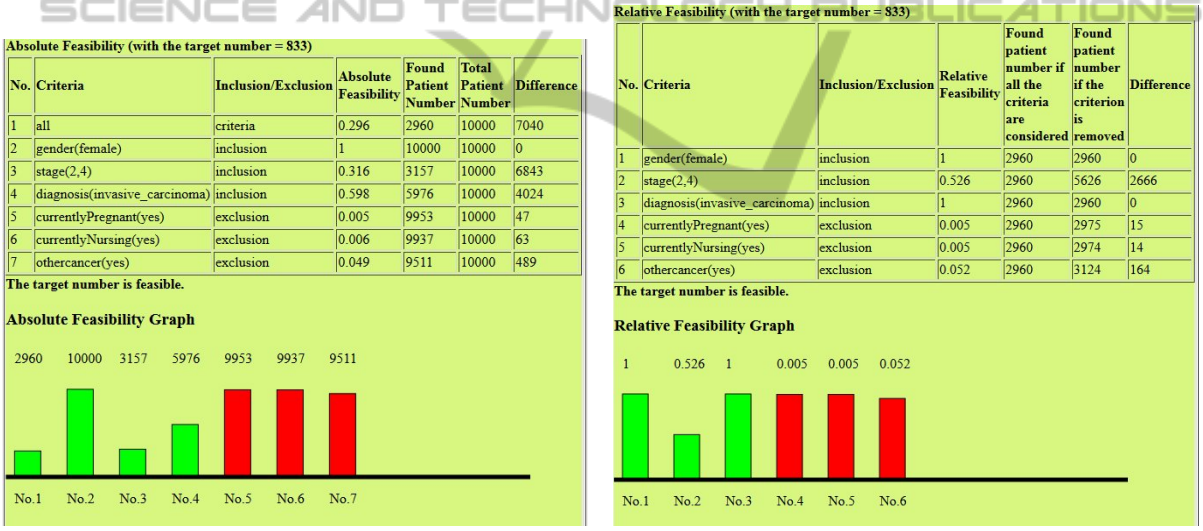
The experiment result shows that the target number is feasible with the absolute feasibility values shown in Figure 6(a). Actually the system finds 2960 eligible patients for those criteria from the 10,000 patients in dataset ZSH2013A. Notice that 'gender(female)' has an absolute feasibility of 1, which means that all patients satisfy this condition. In the absolute feasibility graph shown in Figure 6(a), a high score on an inclusion criterion means that the criterion alone is not very selective, in other words most patients are included. Similarly, a high score for an exclusion criterion means that only very few patients are excluded only based on that particular criterion, for instance only 47 patients are excluded by only taking into account the pregnancy condition.

Figure 6(b) shows the *relative* feasibility rates of the same experiment. This already reveals the more discriminative power of relative feasibility: the absolute feasibility of the 'diagnosis(invasive_carcinoma)' criterion (figure 6(a)) seems to suggest that this is a strongly selective criterion (an absolute feasibility of

[3]from http://clinicaltrials.gov/
[4]http://clinicaltrials.gov/
[5]http://www.maastro.nl/
[6]http://wasp.cs.vu.nl/apdg/download
[7]http://www.cancerdata.org

Table 1: Experiments of Trial Feasibility. PD=patient data set, CS=cohort size, TN= target number, EP=eligible patient, C = total number of criteria, IC = nr. of inclusion criteria, EC = nr. of exclusion criteria, AF = absolute feasibility, F=feasible, ZSH=ZSH2013A, MST=MST2013A.

No.	PD	TrialTemplate	CS	TN	C	IC	EC	EP	AF	F	Modified Criteria
1	ZSH	NCT00001385	200	833	6	3	3	2960	0.2960	yes	none
2	ZSH	NCT00001385	800	3333	6	3	3	2960	0.2960	no	none
3	ZSH	NCT00001385	800	3333	6	3	3	5626	0.2960	yes	stage(2,4)⇒stage(1,4)
4	ZSH	NCT00002720	200	833	7	7	0	468	0.0468	no	none
5	ZSH	NCT00002720	200	833	7	7	0	628	0.0628	no	age(65,80)⇒age(45,80)
6	ZSH	NCT00002720	200	833	7	7	0	1069	0.1069	yes	age(65,80)⇒age(45,80), stage(1,1)⇒stage(1,2)
7	ZSH	NCT00005079	200	833	8	4	4	309	0.0309	no	none
8	ZSH	NCT00005079	200	833	8	3	4	5421	0.5421	yes	menopausal(premenopausal)-,
9	ZSH	NCT00005079	200	833	8	4	4	1013	0.1013	yes	menopausal(premenopausal)-, age(30,50)+
10	MST	MST0000IRMA	200	833	9	5	4	1164	0.3510	yes	none
11	MST	MST0000IRMA	300	1250	9	5	4	1164	0.3510	no	none
12	MST	MST0000IRMA	300	1250	9	5	4	1182	0.3570	no	wellbeing(0,2)⇒wellbeing(0,3)
13	MST	MST0000IRMA	300	1250	9	5	4	1264	0.3820	yes	wellbeing(0,2)⇒wellbeing(0,3), t(0,3)⇒t(0,5)
14	ZSH	MST0000IRMA	200	833	6	3	3	2633	0.2630	yes	none
15	ZSH	MST0000IRMA	800	3333	6	3	3	2633	0.2630	no	none
16	ZSH	MST0000IRMA	800	3333	6	3	3	3500	0.3500	yes	t(0,3)⇒t(0,5)



Absolute Feasibility (with the target number = 833)

No.	Criteria	Inclusion/Exclusion	Absolute Feasibility	Found Patient Number	Total Patient Number	Difference
1	all	criteria	0.296	2960	10000	7040
2	gender(female)	inclusion	1	10000	10000	0
3	stage(2,4)	inclusion	0.316	3157	10000	6843
4	diagnosis(invasive_carcinoma)	inclusion	0.598	5976	10000	4024
5	currentlyPregnant(yes)	exclusion	0.005	9953	10000	47
6	currentlyNursing(yes)	exclusion	0.006	9937	10000	63
7	othercancer(yes)	exclusion	0.049	9511	10000	489

The target number is feasible.

Absolute Feasibility Graph

Relative Feasibility (with the target number = 833)

No.	Criteria	Inclusion/Exclusion	Relative Feasibility	Found patient number if all the criteria are considered	Found patient number if the criterion is removed	Difference
1	gender(female)	inclusion	1	2960	2960	0
2	stage(2,4)	inclusion	0.526	2960	5626	2666
3	diagnosis(invasive_carcinoma)	inclusion	1	2960	2960	0
4	currentlyPregnant(yes)	exclusion	0.005	2960	2975	15
5	currentlyNursing(yes)	exclusion	0.005	2960	2974	14
6	othercancer(yes)	exclusion	0.052	2960	3124	164

The target number is feasible.

Relative Feasibility Graph

(a) Absolute (b) Relative

Figure 6: Absolute and relative feasibility of experiment no.1.

just under 0.6). However, the relative feasibility from figure 6(b) shows that in fact, in the light of the other criteria, its selective power is nil (a relative feasibility rate of 1). This is so because the staging criterion ('stage(2,4)') already implies that the diagnosis must be an invasive carcinoma. Thus, the relative feasibility rate of 1 reveals that strictly speaking, the diagnostic eligibility criterion in trial NCT00001385 is superfluous.

In the second experiment (the second row of Table 1), we change the cohort size from 200 into 800. That results in a new target number of 3333. It is easy to see that the trial is not feasible with this new target number, because 2,960 patients are eligible. Thus, we have to change some criteria to make this trial feasible. From the list of absolute feasibility rates, we see that both the staging criterion and the diagnostic criterion have small absolute feasibility rates, seemingly implying that changing either of them might result in a higher recruitment rate. However, as explained above, looking at the relative feasibility rates reveals that the diagnostic criterion is already implied by the other criteria, and hence changing the diagnostic criterion is unlikely to have much effect on the recruiting

rate, and only the staging criterion is a good candidate for revising the trial definition in order to obtain the required target number of patients.

Thus, in a new experiment (experiment no.3), we change the criterion 'stage(2,4)' into the criterion 'stage(1,4)', which leads to a bigger set of 5626 eligible patients, which exceeds the target number of 3333 patients, and which therefore makes the trial feasible.

Similar experiments are done with a trial at the MAASTRO clinic (trial no. MST0000IRMA) using the data on actual MAASTRO patients (patient data set MST2013A, experiment nr. 10-13) and the virtual data set ZSH2013A (experiment nr. 14-16). The scenarios in those experiments again tell us that it is more useful to check the relative feasibility if we encounter multiple options to change criteria. The relative feasibility exposes those criteria which have been implied by other criteria, or which are inconsistent with other criteria, so that we can focus on redesigning the criteria that have a relative feasibility rate lower than 1.

For example, Figure 7(a) and Figure 7(b) show the absolute and the relative feasibility respectively for the experiment of trial MST0000IRMA over the MAASTRO patient data with the target number 1,250 (Experiment No. 11). Figure 7(b) makes it quite clear that we should modify the criteria about tumor size ('t(0,3)') and wellbeing to increase trial feasibility.

Table 2 shows the list of the maximal and minimal values for absolute and relative feasibility in our 16 experiments. In the table, RF=1 (AF=1) denotes the number of criteria for which the relative feasibility (absolute feasibility) is 1. In the other columns, AF and RF stand for absolute and relative feasibility, while I and E stand for inclusion and exclusion criteria. Thus, maxAF(I) is the maximal absolute feasibility value for inclusion criteria, and similar for the other columns.

6 FINDINGS

Our experiments reveal a number of interesting findings.

Redundant Criteria. First, *every* trial in our testset contains inclusion criteria whose relative feasibility equals 1 (second column of table 2). In fact, all of the trials we looked at have even multipe of such inclusion critera, with the exception of trial no. 9, which has just one. In other words: when measured over realistic patient data, every one of the realistic trials that we looked at contains criteria that are strictly speaking superflous, because when removed from the trial definition, the same set of realistic patients would have been recruited anyway (see proposition 4). To emphasise: all of our trials are real definitions, and this effect was also observed in our experiments on actual patient data.

For exclusion criteria, essentially the same was observed, namely allmost all trials have at least one exclusion criterion with value 0 (again, see proposition 4). The exceptions are trials 1, 2 and 3. But more importantly, all tests on actual patient data reveal exclusion criteria that were redundant for that patient population.

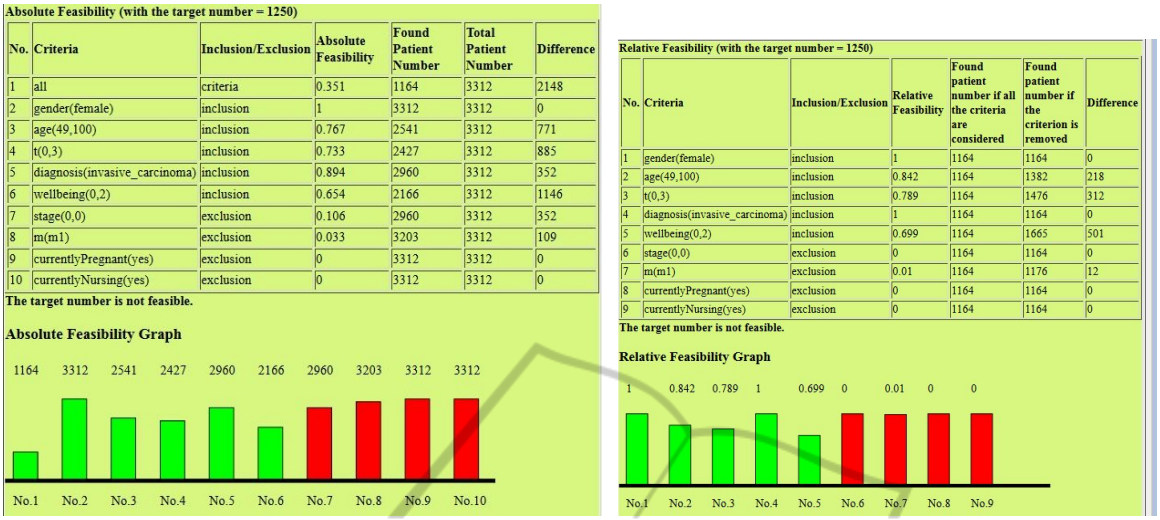
We can only conclude that there must have been other reasons for including these logically superflous criteria in the trial definitions, such as to include a redundant backup test, or for explanatory purposes, or to deal with very rare cases that did not happen to occur in the patient populations on which we determined the feasibility estimates.

Relative Feasibility is more revealing than Absolute Feasibility. Remember that the presence of such redundant criteria could be read of in table 2 from the 2nd column (for inclusion criteria) and from the last column (for exclusion criteria). However, notice that the same effect is *not* revealed by looking at the *absolute* feasibility rates: none of the figures in the columns minAF(I) displays a 1, and none of the fiures in the column maxAF(E) displays a 0. In other words: even though on the *entire* population, all criteria have an actually selective effect, this is *not* the case when the criteria are considered in the context of the other criteria.

This makes us speculate that the redundant criteria were actually included unwittingly, because their no-filtering effect can only be seen in the context of the filtering effect of the other criteria, which is a complex analysis for a human to perform, but which is exactly what our relative feasibility computes.

Inclusion Criteria more Selective than exclusion Criteria. Secondly, it turns out that in real trials, the selective power of inclusion criteria is much greater than the selective power of exclusion critera. The change that can be obtained by removing an inclusion criteria, determined by the minimal value of RF(I), is often around 0.66 mark, meaning that the old population makes up 2/3rd of the new population, in other words: removing an inclusion criterion may increases the recruitment rate by as much as a third. For exclusion criteria on the other hand, we should look at the maximal value of RF(E), which never gets above 0.1, and is often lower. This means that removing an inclusion criteria can only get us a 10% increase in the recruited population at most (again, using real trial conditions and realistic patient data).

Thus, removing an inclusion criterion can have a much larger effect on the recruiting rate than removing an exclusion criterion. It would be interesting to



Absolute Feasibility (with the target number = 1250)

No.	Criteria	Inclusion/Exclusion	Absolute Feasibility	Found Patient Number	Total Patient Number	Difference
1	all	criteria	0.351	1164	3312	2148
2	gender(female)	inclusion	1	3312	3312	0
3	age(49,100)	inclusion	0.767	2541	3312	771
4	t(0,3)	inclusion	0.733	2427	3312	885
5	diagnosis(invasive_carcinoma)	inclusion	0.894	2960	3312	352
6	wellbeing(0,2)	inclusion	0.654	2166	3312	1146
7	stage(0,0)	exclusion	0.106	2960	3312	352
8	m(m1)	exclusion	0.033	3203	3312	109
9	currentlyPregnant(yes)	exclusion	0	3312	3312	0
10	currentlyNursing(yes)	exclusion	0	3312	3312	0

The target number is not feasible.

Absolute Feasibility Graph

Relative Feasibility (with the target number = 1250)

No.	Criteria	Inclusion/Exclusion	Relative Feasibility	Found patient number if all the criteria are considered	Found patient number if the criterion is removed	Difference
1	gender(female)	inclusion	1	1164	1164	0
2	age(49,100)	inclusion	0.842	1164	1382	218
3	t(0,3)	inclusion	0.789	1164	1476	312
4	diagnosis(invasive_carcinoma)	inclusion	1	1164	1164	0
5	wellbeing(0,2)	inclusion	0.699	1164	1665	501
6	stage(0,0)	exclusion	0	1164	1164	0
7	m(m1)	exclusion	0.01	1164	1176	12
8	currentlyPregnant(yes)	exclusion	0	1164	1164	0
9	currentlyNursing(yes)	exclusion	0	1164	1164	0

The target number is not feasible.

Relative Feasibility Graph

(a) Absolute (b) Relative

Figure 7: Absolute and Relative Feasibility in Experiment No. 11.

Table 2: Absolute Feasibility and Relative Feasibility (max and min).

No.	RF=1	AF=1	maxAF(I)	minAF(I)	maxAF(E)	minAF(E)	maxRF(I)	minRF(I)	maxRF(E)	minRF(E)
1	2	1	1	0.316	0.049	0.005	1	0.525	0.052	0.005
2	2	1	1	0.316	0.049	0.005	1	0.525	0.052	0.005
3	3	1	1	0.598	0.049	0.005	1	1	0.049	0.005
4	4	2	1	0.282	n/a	n/a	1	0.474	n/a	n/a
5	3	2	1	0.282	n/a	n/a	1	0.005	n/a	n/a
6	3	2	1	0.495	n/a	n/a	1	0.490	n/a	n/a
7	3	1	1	0.07	0.049	0.005	1	0.057	0.086	0
8	3	1	1	0.576	0.049	0.005	1	1	0.049	0
9	1	1	1	0.195	0.049	0.005	1	0.187	0.053	0
10	2	1	1	0.654	0.106	0	1	0.699	0.01	0
11	2	1	1	0.654	0.106	0	1	0.699	0.01	0
12	2	1	1	0.668	0.106	0	1	0.71	0.012	0
13	2	1	1	0.668	0.106	0	1	0.611	0.014	0
14	3	1	1	0.598	0.402	0.005	1	0.657	0	0
15	3	1	1	0.598	0.402	0.005	1	0.657	0	0
16	2	1	1	0.598	0.402	0.005	1	0.781	0	0

speculate why this is the case, but it is certainly important to have this knowledge when designing trials.

7 CONCLUSIONS AND FUTURE WORK

In this paper, we have developed a lightweight model of trial feasibility. Our model distinguishes the traditional notion of absolute feasibility from a new notion of relative feasibility. Absolute feasibility simply determines the number of eligible patients of a criterion. Relative on the other hand computes how the removal of a single criterion from a set of criteria affects the recruiting rate of the remaining criteria. In other words, absolute feasibility measures the selectivity of a single criterion in isolation, while relative feasibility measures the selectivity of a criterion *in the presence of the other criteria.*

We have implemented our lightweight mathematical model as part of the SemanticCT system, and have used it to determine the relative feasibility of different criteria for a number of different real-life trials, on both actual and synthetic (but realistic) patient data.

Every trial we looked at contains criteria that could have been safely removed from the trial without loss of specificity, a result that could not have been found by using only the classical absolute feasibility measure. To us, this is an unexpected result. Furthermore, it seems that inclusion criteria typically contibute much more to the specificity of a trial then exclusion criteria. Although not unexpected, this result again can only be revealed by using our new relative feasibility estimator.

Future Work. There is a lot of future work to make our simple mathematical model more useful in actual practice. Perhaps the most urgent issue is that the proposed model does not consider missing values of patient data. In the future, both the formal model and the SemanticCT tool will be adjusted to deal with such missing values. That can be achieved by two options: either by introducing credulous and skeptical upper- and lowerbounds for missing values, or by estimating likely values from other patient data.

Many more additional functionalities can be envisaged, such as: i) the ability to download existing trials (e.g. those from clinicaltrial.gov and/or linkedct.org), ii) show more information for each selected criterion (e .g. value distribution in selected cohort data), iii) advanced visualization of the selected cohort data as a colored matrix of criteria x patients, and as a stem-and-leave diagram integrated with a query builder from other tools.

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