Original Research Article

The value of clinical trial medication and yearly medicine cost avoidance from clinical trials conducted by the pharmaceutical industry in Finland

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ABSTRACT

Background: Clinical trials have been reported to cause medication cost avoidance (MCA) for hospitals and societies, but there are no studies documenting MCA from the Nordic countries or from the pharmaceutical industry perspective.
Methods: Three different methods were tested for determining the yearly MCA in clinical trials conducted by the pharmaceutical industry in Finland. MCA was evaluated with questionnaires to pharmaceutical companies operating in Finland in 2001, 2009 and 2013.
Results: In method 1 (year 2001), the MCA in Finland was 70.3 million euros in wholesale price and 50.9 million euros when excluding patients receiving placebo treatment. In method 2 (2009), the MCA was 52.0 million euros in wholesale price and 71.0 million euros in out-sale price i.e. including pharmacy fee and tax. The MCA in method 3 (2013) was 47.2 million euros in wholesale price. The collection of data and the MCA calculation was simple in method 1 (response rate 100%). The methods 2 and 3 were more precise but more time-consuming for the respondents, somewhat affecting the response rate (response rates 90% and 72%, respectively).
Conclusions: All three methods covered the majority of industry-sponsored clinical medicine trials (64-100%) representing 59-63 % of all clinical trials conducted in Finland in those years. Regardless of the methods, the study medications provided by the pharmaceutical industry promoted significant cost saving for the society. We recommend method 1 for a general and less time consuming MCA calculation and method 3 for a more precise calculation, to be conducted in survey format and interview.

Keywords: Cost avoidance, Medication cost avoidance, MCA, Industry-sponsored clinical trials, Pharmaceutical industry, Finland

INTRODUCTION

Clinical trials sponsored by the pharmaceutical industry are the corner stone of the development of new medicines. Three out of four clinical trials are industry-sponsored in Finland.[1] Gaining access to medicines during drug development is one of the most valued benefit realized by the communities that host global clinical trials.[2] Other perceived benefits include the development of health care infrastructure, exposure to external expertise, and the benefit for the local economy.[2] Cost avoidance occurs when trial subjects obtain their medication free of charge

during trials and limited costs for the treatment is incurred by the community or the patient during the trial period. Several terms have been used for the cost avoidance, such as medication cost avoidance (MCA), drug cost avoidance (DCA), pharmaceutical cost avoidance, economic benefit and value of clinical trial medication. In this study we use the term MCA. A variety of studies with numerous methods have been conducted to investigate MCA during clinical trials. These studies have been conducted predominantly in the hospital environment at a single institution and have concerned single therapy areas.[3-10] There are no previous MCA studies using clinical trial data provided by the pharmaceutical companies. There is limited information about studies that comprehensively cover multiple therapeutic areas on a national level.[11] Pharma Industry Finland (PIF) is an association representing the research-based pharmaceutical industry in Finland including also some Contract Research Organisation (CRO) companies as members. PIF has collected extensive data on clinical trials conducted by its member companies since 1995. The aim of this study was to calculate MCA based on data obtained from the pharmaceutical companies operating in Finland and to descriptively compare three different calculation methods to determine MCA in years 2001, 2009 and 2013.

METHODS

Closed survey questionnaires were compiled by Pharma Industry Finland (PIF) experts and authors of this paper MB 2001, 2009, 2013 and NT 2009, 2013. For year 2001, the questionnaires were sent via regular mail and the responses were received by mail or fax. In 2009 and 2013 the questionnaires were sent via email with a Webropol link (Webropol Oy, Finland). The questionnaires were sent out in February following the year of interest and the response time was normally 2-3 weeks. E-mail or phone call reminders were used, when deemed necessary. When the information was insufficient or unclear, additional information was requested from the respondents. No incentives were offered to provide the survey results. The data were obtained from PIF member companies. However, the questionnaire was also sent to non-member pharmaceutical companies and CROs in Finland for the 2009 and 2013 calculations in an attempt to include as many industry-sponsored trials as possible.

The proportion of industry-sponsored trials covered by this study was also compared to the number of clinical trial applications handled by the Finnish Medicines Agency, FIMEA, in the same year (Figure 1). It should be noted that the possible MCA obtained from academic trials (investigator-initiated trials) were not included in this study (Figure 1).
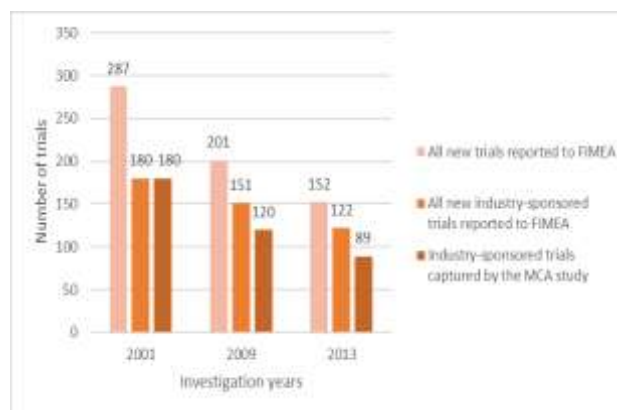

Figure 1. The number of new clinical medicine trials in 2001, 2009 and 2013 visualizing the proportion of trials captured in the MCA calculations. For 2001, MCA calculation was based on all ongoing trials, including new trials (total 523 trials).

In this study, we focused on three different MCA calculation methods used in three specific years. The respondents were requested to report the number of newly started and ongoing clinical medicine trials they had sponsored in each investigation year. The trials were categorized by Anatomical Therapeutic Chemical Classification system (ATC) and by the trial phase. Wholesale prices were used in the calculations.[12] In 2009, also the out-sale prices were used for MCA calculations. The trial subjects in the phase 1 trials with healthy volunteers were omitted from the calculation in 2001, 2009 and partially in 2013, if there were no cost savings expected for their participation in the trials. The number of trial participants for trials that started during the investigation year was used for the MCA calculation in methods 2 and 3. In method 1, the number of trial participants were collected from trials that were ongoing during that year, regardless when the trials had started. Detailed description of the data collected in each year are presented in (Table 1).

Calculating the cost of trial medication in the ongoing clinical trials in Finland in 2001 (method 1): In 2001, the financial benefit to the hospitals of conducting pharmaceutical industry-sponsored clinical trials was calculated, in addition to the educational and scientific aspects of conducting clinical trials. The information for the retrospective cost analyses was collected on paper and the final calculations of MCA were performed using Microsoft Excel (Microsoft Corporation, USA) according to Equation mentioned below. The assumed average maintenance dose per day for a medication used for its main indication in adults (DDD) was used. The wholesale prices, excluding the tax and pharmacy costs were used. The arithmetic mean prices of the medicines in the market were obtained from the Finnish Pharmaceutical Data Ltd, Medula database, Finland.

$$MCA\ 2001 = number\ of\ patients \\ \times duration\ of\ treatment\ \times dose \\ \times dosing\ interval \\ \times average\ price\ of\ drug\ as\ DDD$$

Calculating the cost of trial medication in the clinical trials that started in Finland in 2009 (method 2): In 2009, there was a need to update the MCA calculations and estimate the overall cost savings from clinical trials in Finland. The questionnaire and the calculations were repeated, but with a different approach. The information was collected in a matrix, where the respondent could give the required information (trial medication, dose number of patients) per trial. The information (Table 1) was collected by Webropol and the final calculations were performed using Microsoft Excel according to Equation mentioned below. The MCA was calculated using September to October 2010 prices in Finland (Finnish Pharmaceutical Data Ltd, Medula database, Finland) both for wholesale prices and for out-sale prices. The ATC 5th level API of the reference medication was used, if available.Otherwise the arithmetic mean price of ATC 4th level chemical subgroup information of the reference medication was used.

$$MCA\ 2009 = (n_1 1 \times t \times p_1) + (n_2 \times t \times p_2)$$

Where n_1=number of patients using study medication, t = average duration of treatment, p_1=average price for treatment, n_2=number of patients using comparator, p_2 = average price for comparator.

Table 1: Data collected from the questionnaires to pharmaceutical industry representatives.

Parameters	2001 (method 1)	2009 (method 2)	2013 (method 3)
Trial types	All FIMEA-approved Phase I-IV clinical medicine trials which were ongoing in year 2001, regardless of the initiation year	All FIMEA-approved phase I-IV clinical medicine trials initiated during 2009	All FIMEA-approved phase I-IV clinical medicine trials initiated during 2013
Number of study sites	3005 (includes all open sites in the investigation year, regardless of the trial initiation)	1675 (includes all open sites in the investigation year, regardless of the trial initiation)	928 (includes all open sites in the investigation year, regardless of the trial initiation)
Study medication treatment time (Maximum treatment duration per investigation year was 365 days)	Actualized durations of the treatments	Estimated duration of the treatment per patient as defined in the protocol, maximum 365 days. If the treatment was less than a year, that time was used. If the treatment was in certain periods (e.g. cancer treatments with cycles), only the number of periods was used.	Estimated duration of the treatment per patient (in days) was collected, maximum 365 days. If the treatment was less than a year, that time was used. If the treatment was in certain periods (e.g. cancer treatments with cycles), only the number of periods was used.
Study medication categorization	ATC 2nd level for all medicines in that group	ATC 5th level API of the standard treatment product (or the actual study medication with marketing authorization). ATC 4th level of the standard treatment product for the placebo	ATC 3rd level for the study medication, the placebo and the standard treatment product
Study medicine exposure	Daily dose	Daily dose	Daily dose
	Duration of treatment	Duration of treatment	Duration of treatment
	Dosing frequency	Dosing frequency	Dosing frequency
Patients included in MCA calculation	Number of patients in active treatments and in placebo treatments	Number of patients in active treatments	Number of patients in active treatments and partially patients in placebo treatments
Patients on placebo treatment included in MCA?	Yes	No	Percentage of patients on placebo treatment was evaluated. Number of patients on placebo treatment was included conditionally.
Additional treatments included in MCA calculation	No	API, dose and dosing frequency of the possible additional treatments	No

Continued.

Parameters	2001 (method 1)	2009 (method 2)	2013 (method 3)
Number of included trials which started during the investigation year and participants recruited/ to be recruited during that year (Data in 2001 not used in MCA calculations)	180 trials, number of participants not collected	120 trials, 6535 participants	89 trials, 6139 participants
Number of included trials ongoing during the investigation year and participants recruited (Data in 2009 and 2013 not used in MCA calculations)	523 trials, 58282 participants	475 trials, 94965 participants	284 trials, 30665 participants
Study medication prizing	Wholesale prices (excluding taxes and pharmacy costs) of DDD	Both in wholesale prices (excluding taxes and pharmacy costs) and in out-sale prices (including taxes and pharmacy costs) of DDD	Wholesale prices (excluding taxes and pharmacy costs) of DDD

DDD-the assumed average maintenance dose per day for a drug used for its main indication in adults. API-active pharmaceutical ingredient, FIMEA-Finnish Medicines Agency, ATC-Anatomical Therapeutic Chemical Classification, MCA, Medication cost avoidance.

Calculating the cost of trial medication in the ongoing clinical trials in Finland in 2013 (method 3): In the 2013 questionnaire, a third alternative way of calculating a more precise value of trial medication was used. The information was collected in a matrix, where the respondent could give the required information (trial medication, dose, number of patients) per trial. The information was collected by Webropol and the final calculations were performed using Microsoft Excel according to Equation mentioned below. The inclusion of placebo patients into the calculation was evaluated case by case, depending on the indication, would the patient have received medication if not in the trial. The price calculation of the trial medication was based on the the price in Finland in September to October 2013 and the wholesale price of the package (if available) or on the average value of all package prices in Finland at that time (Finnish Pharmaceutical Data Ltd, Medula database). In addition, the exact dosing interval was used; how many times per day, per week or during the trial the patient received the medication during their participation.

$$MCA\ 2013 = (n_1 1 \times t \times p_1) + (n_2 \times t \times p_2)$$

Where n_1=number of patients using study medication, t = average duration of treatment, p_1=average price for treatment, n_2=number of patients using comparator, p_2 = average price for comparator.

RESULTS

All major pharmaceutical research companies submitted their responses to the yearly questionnaires. The response rate of companies in 2001 was 100 % and in 2009, 89.7 %. In 2013, the response rate was 71.8 %. However, in that year, only 46.2 % of the respondents also filled in the details required for the MCA calculation (Table 2). When the number of trials reported in the questionnaires were compared with the yearly clinical trial applications submitted to FIMEA by the industry, the analyses represented 100% (2001), 79.5% (2009) and 73.0% (2013) of all industry-sponsored clinical medicine trials conducted in Finland during those years (Figure 1).

Table 2: Number of respondents to the questionnaire.

Parameters	2001 (method 1)	2009 (method 2)	2013 (method 3)
Percentage of responding pharmaceutical companies operating in Finland	43/43 = 100%	35/39 = 89.7%	28/39 = 71.8%
Proportion of annual industry-sponsored trials captured by the questionnaire	100%	79.5%	73.0% for the overall questionnaire For MCA questions, 18 companies (46.2%) filled in the details required for the MCA calculation

Table 3: Medication cost avoidance by ATC group for the three largest ATC groups reported in trials in 2013 in wholesale price.

Indication (ATC)	MCA 2013 in Finland
Cancer	43.59 million euros
Central nervous system	0.12 million euros
Vaccines	1.31 million euros

ATC, Anatomical Therapeutic Chemical Classification system

FIMEA categorize the trials as commercial and non-commercial. Trials are considered non-commercial if the investigator receives no commercial funding other than potentially free trial medication. The calculated MCA in 2001 (method 1) was 70.3 million euros in wholesale price for all participants in phase II-IV trials including patients receiving placebo and 50.9 million euros when the proportion of trial patients receiving a placebo treatment were excluded. The total calculated MCA in 2009 (method 2) was 52.0 million euros in wholesale price and 71.0 million euros in out-sale price i.e. including pharmacy fee and tax. The price for possible additional medication was calculated similarly. It was 20 477 euros in wholesale price and 32 883 euros in out-sale price. The MCA calculation in 2013 (method 3) was the most detailed. The value of the trial medication was 47.2 million euros in 2013, given that all planned patients were recruited. This MCA was mainly based on cancer trials as the majority of the information provided was related to cancer trials (Table 3).

DISCUSSION

The MCA was calculated using three different methods. Because of the differences among the methods, it was only possible to compare them descriptively. Extrapolation of the results was not considered meaningful in our study, which aimed to calculate a national level MCA with data covering trials in multiple therapy areas with multiple types of medicines. Extrapolation was not justified as the MCA is strongly dependent on the indication/ATC and the result would thus be biased when there is no information of the missing trials. The MCA varied from 47 to 70 million euros between the methods described. The main reasons for the different results were, in addition to the differences in the number of patients and indications, the inclusion of either ongoing trials (method 1) or trials scheduled to start during the investigation year (methods 2 and 3). Also the level of ATC used impacted on the result, as the prices in ATC level 2 were lower and more inaccurate than in ATC levels 3,4 or especially 5, due to the numerous number of old generic medicines.

In 2001, the response rate was 100%, which is extremely unusual. This maximum response rate was possible, as all pharmaceutical companies and CROs conducting clinical trials were PIF members and they were obliged to answer member surveys. Some responses were obtained after three reminders. At that time, there was also a need to demonstrate the importance of trials conducted by the pharmaceutical industry, which motivated the companies to respond. In 2009 and 2013, the situation had changed, as the pharmaceutical industry had become more fragmented and not all companies nor CROs operating in Finland were members of PIF. Therefore some non-member companies were also invited to participate in the questionnaire. The 2009 and 2013 response rates were 89.7% and 71.8%, respectively. More important than the response rates of the companies, the main indicator for a reliable national-level MCA was the proportion of all industry-sponsored trials in Finland that could be captured by the questionnaires. In our study, MCA calculations represented 100%, 79.5% and 46.2% of the industry-sponsored trials in years 2001, 2009 and 2013, respectively. Even with the response rate of 46.2 %, we consider the calculations provide comprehensive national estimate on MCA for industry-sponsored trials, because the responses mostly covered cancer trials (Table 3) which normally have the most expensive medications. As academic clinical trials were not included and because up to a half of the industry-sponsored trials were not captured in 2009 and 2013, in reality, the MCA is higher than calculated with all the three methods. Although the number of patients in academic trials are generally rather small, the cost saving might still be significant for the hospitals, if the medication is provided free by pharmaceutical companies. This study did not contain the trial medication provided free of charge to academic researchers.

When calculating the value of clinical trial medication, the most relevant information was the number of patients per ATC group, the price of the medication in that ATC group and the duration of the treatment. The calculations were mainly performed using the wholesale medicine prices, i.e. excluding pharmacy fees and taxes. The wholesale prices are approximately 60% of the out-sale prices. While the use of wholesale prices is appropriate for trials conducted in the hospitals, for primary care trials the MCA calculation provides a value that is too small, since the out-sale prices of the trial medications should normally be used. With method 1, the MCA was determined using ATC 2nd level average costs of all the medicines in that therapeutic subgroup in ongoing trials 2001. Although the medicines were very diverse at the 2nd level and the prices varied greatly, the use of an upper-level ATC-group reflects the physicians' options to select very different treatments for their patients. It was also much easier to collect the information for the 2nd level than the 4th or 5th level owing to confidentiality issues. In addition, entirely new medicines lack a 4th and 5th level classification, but a

2nd level could be determined. The relative ease of collecting information and the much larger workforce available at that time enabled participants to complete the time-consuming questionnaires (requiring at least an hour). In addition, the close collaboration between MB and the clinical trial experts in the companies were also reasons for 100 % response rate.

The MCA in 2001 was calculated for patients on active treatment (excluding phase I healthy volunteers), as well as for patients receiving placebo. The inclusion of a placebo patient in the MCA calculation reflected the fact that those patients would obtain some medication for their disease if they were not taking part in the trial. In other cases there was no alternative medication, and the patient could be offered an alternative form of treatment e.g., surgery. The calculation using an average price for the ATC 2nd level reduced the monetary value of medication, as there were numerous old and inexpensive medicines available in most ATC groups. Conversely, the strength of this calculation was that it included all patients participating in the trials in 2001, as it was based on ongoing trials. In year 2001, the number of trials was high; 523 trials. The maximum number of days was limited to 365 days. Another benefit of this therapeutic subgroup calculation was that it did not assume that the medicines used would be either the newest or the most expensive. The difference between the calculated 50.9 million euros, if the placebo patient were omitted, and 70.3 million euros, if the placebo patients were included, is very considerable, but the true figure lies between these two values. With methods 2 and 3, the price used was closer to the real value of the study medication. However, the response rates were lower than for the first method, maybe because the questionnaires were more time-consuming to complete. The increased workload of the pharmaceutical industry personnel in general had increased and more complicated clinical trials and non-obligatory response requirement were in place at that time. The second calculation method resulted in a MCA of 71.0 million euros. The value of medicines provided free of charge in addition to the investigational medicinal products was small, 20,477 euros inwholesale price and 32,883 euros in out-sale price. In method 2, it was assumed that the patient would receive the reference product for their disease if they were not participating in the trial. Therefore, the cost saving for society was calculated using the price of the factual reference medication or, if this was not available, with an average price of the corresponding ATC group 4th level chemical subgroup. The weakness of this method was that it was based on recruitment projections in trials, not on actually recruited patients. In reality, the number of recruited patients can differ markedly from the planned number, frequently being less than intended. The factual financial effect of the trials started in 2009 was, thus, most probably somewhat less than the calculated value. Conversely, the calculation covered 79.5% of the industry-sponsored trials and 59.7% of all trials conducted that year, which compensates for the slight over-estimate of the national MCA value.

The third MCA calculation method was the most detailed when compared to methods 1 and 2. The calculation was based on the intended number of trial subjects that would be recruited in Finland, causing the same weakness in the method as previously described for method 2. The value of the MCA was 47.2 million euros and covered 46.2% of the industry-sponsored clinical trials in Finland so the factual MCA is much higher. Method 3 was challenging to report and calculate as it tried to reflect the true value of the medication and thus numerous extra enquiries were necessary to obtain the correct doses and durations of treatments. The aim of this method was to obtain an exact value of MCA, but it was noted that this could not be accomplished through the use of a questionnaire: its use was difficult to explain to the respondents and it was challenging to cover all aspects of incurred costs. Some of the challenges could be solved by conducting an interview study, instead of a questionnaire. Thereby, more detailed values could be obtained facilitating more complex and detailed calculations. The table used for the calculation should be sent to the respondents in advance together with a detailed explanation of the aim and requirements of the interview study. The requested items could be explained and all detailed information could then be determined during the interview. The questionnaire needs to be well structured and only the most important items should be requested. As the trial medication does not have an associated price unless it has a marketing authorization, information of the reference medication and the ATC 3rd or ATC 4th level of the study medication are required. For the total cost of the study medication, the price of the tablet/injection/dose or the total number of tablets/injections/doses for the study participants during the entire trial (this also considers e.g. cancer trials with treatment cycles) should be collected when known. Additionally, in trials with marketed products the sponsor can provide the MCA directly (price per dose x number of doses x number of trial participants). The MCA for patients receiving a placebo, should be omitted, unless it is considered relevant for that indication or otherwise considered necessary by the respondent. In interviews both the respondent and the person performing the MCA calculation will perceive the overall picture and the response is obtained without extra correspondence. For the interview, a pilot would be required to ensure that the study is explained properly, and the table or questionnaire could be revised to improve the accuracy of the data provided and derived. As the MCA was mainly based on cancer trials, one could also consider to restrict the calculation to cancer or a few indications. The number of trial participants in the vaccine trials was 23,268 and therefore the MCA was significant despite the moderate price for a single vaccine (Table 3). Previous studies on MCA calculations have been conducted mainly in the hospital environment concerning single research units or with a single therapeutic area. The therapeutic areas have varied, at least half of them concentrating on oncology trials. This is understandable, as oncology remains the most significant area of research with often expensive treatments. In our 2013 calculation cancer medication was

43.6 million euros out of 47.2 million euros, representing 92% of the overall MCA.[13]

The variation of MCA study designs in previous studies hinder the closer comparison to our study. One national study was conducted in Hungary in 2010.[11] The researchers assessed a randomly selected sample of 50 trials submitted to the National institute of Pharmacy. In their study the MCA was 67.0 million US dollars covering all 248 clinical trials initiated in Hungary in 2010. That method was similar to method 2 we used in this study; however, they calculated a fraction of 50 trials and extrapolated to the total MCA, whereas we did not extrapolate our data. In addition, the Hungarian MCA study was based on trials started in the investigation year. The strength of our study is that we tested three different methods and their usability within one country and with wider range of therapy areas and study sites than in previous studies. Even if the method designs did not allow further statistical comparisons between the methods, this way we obtained unique data for comparing different aspects of MCA calculations. Another strength is that we have used the data provided by the pharmaceutical companies. They were able to collect data on their ongoing and initiated trials, number of patients, prices of the medications and the indications studied. All methods contained inaccuracies, but we believe that the data obtained from the companies is the most accurate available. An additional strength is that our calculation is based on detailed data collected and not partially extrapolated. The investment in Research and Development (R&D) in Finland by the pharmaceutical industry was 181 million euros in 2001 and 255 million euros in 2009 (data obtained from our questionnaire but outside the scope of this study). Adding the calculated MCA values of trial medication significantly increases the value of the investment in R&D. This investment in medicines R&D creates employment, tax revenue, welfare and savings in the costs of medicines for the society and patients. For some patients the trials provide much more, since they allow them access to high-quality treatment, even life-saving treatments, and extra surveillance. During the investigation years 2001 and 2009, it should be noted that the Finnish state invested 78 and 41 million euros, respectively, in academic clinical trials to improve health care at university hospitals.[14] Thus, MCA and R&D investment by the pharmaceutical industry play a vital role when clinical trials are conducted in Finland.

CONCLUSION

When calculating the MCA using general ATC 2nd level and DDD classification, the collection of data and the MCA calculation was simple. The MCA with method 1 was less than with methods 2 and 3 owing to the use of the ATC 2nd level containing lower prices for numerous older products. Conversely, the response rate was extremely high, compared to the more detailed methods. However, the 100% response rate would probably be unobtainable if method 1 were repeated now. This method can be used to

obtain a general overview of MCA. Methods 2 and 3 were more precise but more challenging for the companies to provide the data and for the researcher to calculate the MCA. When conducting an MCA study containing complex calculations, an interview study, instead, could resolve some of the challenges encountered. Since the trial medication does not have a price unless it has a marketing authorization, the information of the reference medication is required and the ATC 3rd or ATC 4th level group of the study medication. For a more precise MCA calculation we recommend method 3 and its conduction as an interview survey.

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