Improving the drug development process by reducing the impact of adverse events: the case of cataracts considered

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Brief Synopsis: Using simulation modeling, we explored the impact of a novel screening assay to reducing the impact of adverse events during the pre-clinical and clinical trial drug development phases.

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Abstract:

Cataract was used as a model for the prevalence and economic impact of adverse events during the drug development process. Meta-analysis revealed a reported prevalence of cataract of 12.0% (1.0-43.3%), 3.8% (2.4-12.5%), 1.0% (0.0-8.1%), 1.7% (0.0-34.8%) and 3.8% (2.3-5.7%) of compounds in Pre-clinical, Phase I, II, III and IV clinical trials, respectively. Utilizing a human-based in vitro screening assay to predict cataractogenic potential in man could allow better selection of novel compounds at early stage drug development. This could significantly reduce costs and ultimately increase the probability of a drug obtaining FDA approval for a clinical application.

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Background:

Fully assessing the impact of contraindications during the traditional drug development process is notoriously difficult given that the vast majority of "negative studies" remain unpublished. Thus, existing drug development models, while producing compounds which afford clinically significant results for specific indications are also accompanied by adverse events whose treatment and management can be both extensive and expensive. If such adverse events are sufficiently severe, the drug will warrant withdrawal from the market. In the United States, for example, it has been estimated that only between 1 in 5,000 to 10,000 potential compounds receives final market approval by the Food and Drug Administration (FDA) [1]. Problems can also arise during pre-clinical animal trials, which can cessate further development of a given compound. Much of the traditional drug development process is, therefore, fraught with inefficiencies and wasted resources and requires greater refinement in candidate selection as well as greater prediction of targeted effects and the mitigation of harmful adverse events in human beings. Drug-induced cataract is one such significant adverse event for a number of systemic compounds. Moreover, cataract can arise during pre-clinical animal trials, which can result in withdrawal of that candidate from the drug development programme.

Overall, the drug development process is comprised of a number of stages including: pre-clinical (safety and dosing studies on animals) and human clinical trials consisting of Phase I or dose-ranging safety studies, Phase II efficacy and safety studies often against placebo, Phase III efficacy and safety studies with a therapeutic dose and Phase IV or post-marketing utilisation studies of the drug. Thus, the potential for drug failure in clinical trials is an important source of both costs and a range of adverse events, such as cataract [2]. Hay *et al*, for instance, concluded that the success rates of compounds undergoing Phase I trials which ultimately received final registration was only 10% [3]. Given such a high attrition rate for compounds, the high number of adverse events stopping trials from proceeding and the high costs of drug development, it is exceedingly useful to better understand the full magnitude

and costs associated with adverse events during the drug development process as well as the potential role of an early stage screening assay to improve drug candidate selection. To achieve this we assessed cataract as a model outcome as it is a recognised adverse event that can be observed and recorded non-invasively. Cataract also has a specific treatment which has a defined cost associated with its treatment (surgical removal of cataract). More precisely, our aims were twofold: i) to undertake a systematic literature review of the scientific literature on the reported prevalence of cataract as an example of an adverse event amongst compounds undergoing drug development, and ii) using such evidence as gleaned from this systematic review and other sources to develop a simplified economic model to estimate the cost implications arising from possible cataractogenic adverse events during the drug development process as well as to explore the impact of a possible screening assay to reduce the probability of incurring such adverse events.

Methods:

i) Systematic literature search:

The primary research question addressed by the systematic literature search was how prevalent is cataract as an adverse event in the drug development process? The main literature database searched was Google Scholar over the period January 1990 to May 2015 for pre-clinical animal studies and over the period January 2005 to May 2015 for clinical studies in humans. It has elsewhere been shown that Google Scholar provides a high degree of coverage and precision with regards to similar literature search engines, such as PubMed/MED [4]. To find clinical trials, the search strategy involved using terms such as "phase I trial" cataract where trial was replaced with *study* and *clinical* and the phase was varied. Papers mentioning clinical trials in the titles of articles were examined, and the word *cataract* was searched to determine whether cataracts formed as adverse events, or were only mentioned in the introduction, for example. For post-acceptance trials, the search terms *double-blind adverse cataract*

was used, and for animal studies the phrase *preclinical animal adverse cataract* was used. To ensure high levels of evidence from the literature review, the inclusion criteria used to determine the cataractogenic properties of possible compounds were only derived from well conducted randomised clinical trials or case-control studies. Similarly, case series and case report studies were excluded from the analysis.

ii) Economic model:

The economic model was developed in Visual Basic Applications (VBA) Microsoft ® Office Excel (Microsoft Corporation). The input parameters for each phase were imported from a spreadsheet into the VBA macro. These include parameters used to assess the trial itself: the number of patients, the probability of a favourable outcome in each phase of the trial, the reported probability of developing cataract as an adverse event in both the treatment and control groups, the nominal cost per patient for each phase of the trial, the cost of treating cataracts, the time spent in each phase of the trial, the branded drug price, the number of prescriptions written, which was set equal to one million and the discount rate. The model routinely evaluated each patient in the drug development phase, and at each stage there was a defined probability of favourable outcome and progressing to the next phase of the trial. For each patient a uniform random number between zero and one was sampled, and if this random number was less than the probability of a favourable outcome, the number of favourable outcomes was incremented. The same procedure was done for cataracts for each patient. It was possible, for example, for a single patient to develop cataracts but still be cured, thus the probabilities are independent. This evaluation was repeated for each patient in both the treatment and control groups. The trial phase was considered to have passed if: A) the difference between the number of favourable outcomes in the treatment in the control groups was greater than twice the square root of the number of patients (corresponding roughly to p=0·025) and B) the difference between the number of adverse events, was *not* greater than twice the square root of the number, according to the same metric. The economic model assumes that the drug being developed

was for a life-threatening disease, such as, cancer. In such a circumstance, the presence of cataract, as an adverse event, significantly impact a patient's vision and overall quality of life and therefore patients in the model undergo cataract surgery to remedy this. The use of a screening assay which reduces the healthcare costs associated with treating adverse events and the savings to be redeployed towards providing life-saving drugs for an even greater number of patients from the same total fixed healthcare budget are also modelled. Each phase was iterated one thousand times, and the fraction of iterations that passed was taken as the probability of the trial passing. If a trial passed, the excess number of adverse events, that is, cataracts in the treatment group is compared to the control group and is recorded and averaged over all passed trials out of the thousand. The costs were calculated by multiplying this average excess by the cost for cataracts surgery, based on a discount rate compounded annually and applied at the end of the phase. The total cost was calculated as the sum of the nominal costs and the cost of the excess cataracts, and this was divided by the number of sales at a given price in order to calculate the break-even time required to offset the overall cost of the drug trial.

The key direct healthcare costs included in the model are comprised of: i) the cost of the conducting the pre-clinical and human clinical trials of the drug or compound under investigation during each phase of the drug development process (Pre-clinical, Phase I through III, as no trial based costs accrue in Phase IV) [5-6]; and ii) the costs associated with cataract surgery costs for which published reference tariffs from the National Health System (NHS) in the United Kingdom were used [7]. Indirect costs, such as reduced productivity amongst trial participants were excluded from our model, as they are difficult to fully capture. Such indirect costs are, however, likely to be substantial and thus our simplified economic model must be viewed as an underestimate of the full costs associated with developing a new drug. The time horizon of the analysis was that of the entire drug development life-cycle and this was also taken from the literature [8]. The economic model used a discount rate of 3·5% per annum to handle the time preference of money for alternative uses of drug development funds [9]. Lastly, as little data on the

mean value of branded drug prices was available, the mean price of branded drug prices was derived from a review of the average price of branded drug in Canada (found to be CDN $ 80·88 or US$ 65·40), yielding a working branded price of range between US$ 30 to US$ 90 for our simplified economic model [10]. All cost data were converted from local currencies into US dollars.

Results:

i) Systematic literature search

As noted above, Google scholar was the primary tool used for literature research. It searched through scholarly literature, including those publications indexed by other services such as PubMed, using the full text rather than specifically focusing on the title or authors. Papers whose full text could not be accessed from the McGill University Library were excluded unless cataract information was found in the abstract. For each search phrase (eleven in total, three for each stage and one each for pre- and post-clinical), the first sixty results were examined in depth. Towards the sixtieth result, articles were rarely relevant, and no relevant articles were found in the sixty-first through eightieth results, thus only the first sixty were focused on. This led to a total of six hundred and sixty articles that were initially considered for review. Out of these, a total of forty-one papers were examined in detail as they definitively reported on cases of cataracts in the paper.

Our results are stratified according to the various phase of the drug development process. The main findings from the systematic literature search are presented in Tables 1. As can be seen in Table 1, 12.0% (Range: 1.0-43.3%) of animals in the pre-clinical stage developed cataract. Table 1 also presents the impact of small scale Phase I, or safety studies of compounds in humans with an average reported prevalence of cataract of 3.8% (Range: 2.4-12.5%). Many of the systemic compounds reported as causing cataract occurred in conditions such as cancer which were life-threatening. Table 1 similarly highlights the prevalence of cataract among Phase II studies with a figure of 1.0% (Range: 0.0-8.1%). Equally, Table 1 presents the prevalence of cataract among compounds undergoing Phase III clinical

development, finding that the average value was 1.7% (Range: 0.0-34.8%) of compounds. Finally, the later part of Table 1 presents the findings for post-marketing surveillance or Phase IV data on published reports and found that the prevalence of cataract as an adverse event was 3.8% (Range: 2.3-5.7%).

ii) Economic model

The model was implemented using data from the literature search conducted above. The basic assumptions and inputs used in the economic model are presented in Table 2. The probability of developing cataract in each phase of the trial was given by the difference in the probability between the control and treatment groups. In the case of the base case scenario, this was set to the range given by the reported prevalence values obtained in the literature search conducted above. It is estimated that the total cost of completing pre-clinical and clinical trials for a single compound is US$ 32,380,000. Drawing on data collected from the economic model, the financial benefits of a good predictive screening tool for adverse events, such as cataract can be considered on two levels. The first concerns the savings arising from identifying a side-effect in a drug designed to treat a non-life threatening condition. In such cases the drug would normally be withdrawn at some stage from the drug development process. If a drug was hypothetically withdrawn following pre-clinical animal trials, early detection by a screening assay, would save US$ 4,448,162, following phase I clinical trials US$ 5,447,989, at the end of phase II clinical trials US$ 7,095,541, at the end of phase III clinical trials US$ 31,349,265 and after Phase IV some US$ 32,378,610 respectively. An additional scenario relates to drugs that will be used to treat a life threatening disorder; in such cases, a number of adverse events, including cataract, are deemed to be acceptable. Nevertheless, development of an effective drug that does not display an adverse event is still preferable. If a pre-clinical screening assay can lead to an improved drug selection i.e. an efficacious drug independent of a severe adverse event then this could, in the case of potential cataract screening, reduce the overall cost of a trial and reduce the break-even time for a single compound. Table 3 presents these findings and displays the impact which a screening assay might have upon the overall branded

drug price and the break-even time to recover the financial investment made by the manufacturer to develop a new drug. As can be seen given the assumptions of the model, approximately US$ 1,057,349 might be theoretically saved as a result of using some sort of screening assay to discriminate amongst compounds entering the drug development process. Moreover, using a mean branded drug price of US$ 65.40, this translates in to roughly 16,167 extra prescriptions which might be written and potential lives saved, with less adverse events in the process.

Discussion:

i) Systematic review

Despite focusing solely upon cataracts, our review and model is illustrative of the significant impact which adverse events pose to the drug development process and the scope for future improvements. In 2013 alone, for example, it was been estimated that as many as 4.12 million scientific procedures were started on animals in Great Britain alone [11]. Moreover, it has been well documented that animal models translate rather poorly to human models of disease and are such of limited overall utility [12-13]. In this respect, FDA has noted that "... nine out of ten experimental drugs fail in clinical studies because we cannot accurately predict how they will behave in people based on laboratory and animal studies" [14]. Thus, the low probability of being successful in the early pre-clinical animal modelling phase, potentially translates into significant downstream economic costs for drugs which are more likely to be accompanied by multiple adverse events. Lastly, it is likely that if it was possible to include data from unpublished "negative studies" the true prevalence of cataract and indeed of other adverse events in the drug development process would be even higher than have been modelled.

ii) Economic model

Economically, the avoidance of adverse events, such as cataract, in the drug development process is of great importance to individual pharmaceutical manufacturer's being able to maximise the return on their scarce research and development budgets. While it was not possible to obtain direct economic data on

the cost of adverse events due to the clinical drug development process from an industry wide perspective, our model has attempted to predict the economic impact of improvements made as a result of the use of a hypothetical assay or biomarker to screen out compounds likely to produce a single adverse event, namely cataract. *Ceteris paribus*, the use of a screening assay would pay for itself relatively quickly, as drug manufactures would be better able to triage which compounds were more likely to yield promising so-called "on target" effects versus more deleterious "off target" effects and so halt development on less promising compounds earlier on in the drug development process, thereby resulting in direct cost savings which could then be ploughed back into finding ever more refined compounds for clinical development.

iii) The case of cataract considered

Unlike other organ or tissues systems in the human body, the lens presents an isolated tissue system which might enable effective screening biomarkers or assays to be developed. The diversity of physiological response between species is demonstrated by *in vitro* whole lens culture which shows distinct patterns of response to receptor associated ligands in the rat and differs to those observed in human lenses cultured under the same conditions [15]. Moreover, the sensitivity of the lens to various drugs across the species will differ and thus whole lens *in vitro* cultures can be used as one level of predictive testing for adverse side effects for the respective species *in vivo*. Equally, in terms of high throughput screening, human lens cell lines could provide a relatively cheap and efficient system and could serve as a possible predictor for the outcome of human clinical trials. Importantly such screening assays could flag early problems and so avoid needless animal usage and potentially adverse events in human clinical trials at least in so far as systemic compounds causing cataractogenic adverse events are concerned [16]. However, additional consideration should be made regarding the limited blood supply to the lens and the likelihood of specific agents entering the eye and accruing in the ocular humours that bathe the lens [2].

Moreover, such a possible screening assay may well serve to improve the efficaciousness of those drugs which are brought to market and increase the so-called “on-target effects” and so minimise the “off-target effects”. In addition, by avoiding the potential for adverse events, like cataract formation, pharmaceutical manufacturers will be avoiding the downstream costs of treating such adverse conditions should these develop in the context of their human clinical drug trial. This paradigm shift could represent a move towards what might be termed “Informed drug discovery or development” with manufacturers more fully aware that certain compounds are more likely to cause a range of unintended and potentially costly healthcare interventions. Overall, our systematic literature search is necessarily limited given the much larger number of unknowable “negative studies” regarding cataract formation in the drug development process and more should be done to capture these significant missing pieces of the overall puzzle. As such, the development of a cost-effective pre-clinical screening procedure involving human cell/tissue models located in the lens may hold considerable promise in terms of reducing drug induced cataract during the drug development process. This approach could with modification to this and other therapeutic areas provide both economic benefits to companies and importantly improve the wellbeing of millions of patients by producing safer, more efficacious, and more targeted medications with fewer adverse events.

iv) Final thoughts

While our research has focussed on cataractogenic adverse events attributable to systemic compounds and medications, the general principles presented here using cataract as a case study are applicable to other tissues associated with specific adverse events, such as liver toxicity, which impact on animals and humans alike in the drug development process. As demonstrated in our simplified economic model, a relatively modest decrease in the probability of developing cataract within the drug development process reduces not only the costs of conducting the trials, but also the break-even time to recoup outlays

expended on research and development. As researchers in other disease areas have shown there is a need to better understand the translational interplay between rodent and human biomarkers or assays particularly for detecting specific tissue changes relative to baseline levels and potentially targeted therapeutic effects [17-19]. Such tissue-focussed systems would provide a clear signal to encourage drug manufacturers to adopt a much more proactive stance to combat the enormous scale of the problem due to too many drugs with many more “off-target” than “on-target” effects and the accompanying plethora of adverse events, as well as the ever spiralling drug development and healthcare costs due to treating these adverse events.

In the final analysis while drug manufacturers will probably need to be convinced or incentivised to make such dramatic changes in how they bring new drugs to market, novel screening assays already in hand or close to being developed could prove pivotal to bringing new more efficacious pharmaceuticals to market. In an era of both constrained industry research and public healthcare budgets those companies which adopt such screening assays technologies will not only be likely to secure new patents, but are also likely to secure favourable pricing and reimbursement status as well. Let us, therefore, go back to our labs and offices and go forth determined to improve the tools and techniques by which new drugs are discovered, tested, developed, approved and used.

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Copies of the economic model used in this research may be obtained by sending an email to Andrew.Smith@medmetricsinc.com

Contributions

Conceptualization and study design (AFS, IMW), data collection and management (AFS, AK), analysis and interpretation of the data (AFS, AK, IMW), economic modeling (AFS, AK); review and direct input into the manuscript (AFS, AK, IMW); final manuscript preparation (AFS).

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As corresponding author, I had full access to all the data in the study and had the final responsibility for the decision to submit the paper for publication.

Declaration of Interests

AFS and AK are employees of MedMetrics Inc.

Ethics Approval

As this study did not involve direct patient involvement, ethical approval was not sought.

Provenance and peer review

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Legends for Tables

Table 1: Findings from a systematic review detailing the prevalence of cataract according to specific drug development phase

Table 2: Key economic model inputs and assumptions on the overall impact of drug development under both base case and screening assay conditions

Table 3: Key economic model outputs according to branded drug price, break-even time and overall cost of the trial

Table 1:

Study Aim	Compound of interest	Animal used/Phase	Number of animals used	Number of cataract eyes	Prevalence of Cataract % (Range)	Impacted Drug Progression	Reference
Pre-clinical							
Carcigenocity	Tamoxifen	Rats	103	38	36·8	No	[20]
Carcigenocity	Toremifene	Rats	400	4	1·0	No	[21]
Cataract induction	Doxorubicin	Rats	60	26	43.3	No	[22]
Overall Pre-clinical			563	-68	**12.0% (1.0-43.3%)**		
Phase I							
Retinoblastoma With Vitreous Tumor Seeding	Mediated Delivery of Thymidine Kinase Followed by Ganciclovir	I	8	1	12.5	No	[23]
Retinoblastoma	Intra-Arterial Chemotherapy	I	78	2	2.5	No	[24]
Cancer	Tipifarnib and Capecitabine	I	41	1	2.4	No	[25]
Solid tumors and lymphomas	PF-04929113	I	33	1	3.0	**Yes**	[26]
Lung Cancer	Gefitinib with radiation and cisplatin	I	14	1	7.1	**Yes**	[27]
Retinal Degeneration	Ciliary neurotrophic factor	I	10	1	10.0	No	[28]
Myeloma	NVP-AUY922	I	24	1	4.2	No	[29]
Overall			208	8	**3.8 % (2.4-12.5%)**		
Phase II							
Macular edema	Ranibizumab	II	10	0	0.0	No	[30]
Gynaecologic cancers	Ixapebilone	II	49	1	2.0	No	[31]
Retinoblastoma	Intra-arterial chemotherapy	II	78	0	0.0	No	[32]
Macular edema	Dexamethasone	II	997	0	0.0	No	[33]
Lymphomas	Radiation	II	37	3	8.1	No	[34]
Alzheimer's	Bapineuzumab	II	125	5	4.0	**Yes**	[35]
Breast cancer	Gemcitabine	II	68	1	1.5	No	[36]
Lung cancer	Cetuximab and chemoradiation	II	34	1	2.9	No	[37]
Macular Edema	Dexamethasone	II	315	7	2·2	No	[38]
Overall Phase II			1713	18	**1.0% (0.0-8.1%)**		
Phase III							
Dry Eye	Cyclosporine	III	412	3	0.7	No	[39]
Macular Degeneration	Ranibizumab	III	4,300	3	0.0	No	[40]
Macular Degeneration	Ranibizumab & Verteporfin	III	423	11	2.6	No	[41]
Macular Edema	Ranibizumab	III	261	14	5.4	No	[42]
Macular Edema	Ranibuzimab	III	264	5	1.9	No	[43]

Chronic obstructive pulmonary disease	Mometasone furate/formeterol fumarate	III	1,196	6	0.5	Followed up	[44]
Macular Edema	Triamcinolone acetonide	III	43	15	34.8	Followed up	[45]
Macular Degeneration	Ranibizumab	III	249	1	0.4	No	[46]
Macular Edema	Ranibizumab	III	377	3	0.8	No	[47]
Prostate Cancer	Denosumab	III	734	35	4.8	No	[48]
Myeloma	Thalidomide & Prednisone	III	332	6	1.8	No	[49]
Glaucoma	Tafluprost & Latanoprost	III	402	18	4.5	No	[50]
Macular Degeneration	Pegaptanib sodium	III	161	23	14.3	No	[51]
Diabetes	Ezetimibe	III	152	1	0.7	No	[52]
Myeloma	Lenalidomide and low-dose dexamethasone arm	III	1076	38	3.5	No	[53]
Alzheimer's	Placebo	III	1054	12	1·1	No	[54]
Overall Phase III			11,436	194	**1.7% (0.0-34.8%)**		
Phase IV							
Breast cancer	Armiidex and Tamoxifen	IV	9,366	395	4.2	No	[55]
Arthritis	Glucocorticoids	IV	27	1	3.7	No	[56]
Breast cancer	Tamoxifen, Raloxifene, & Aromatas	IV	19,471	707	3.6	No	[57]
Arthritis	Prednisolone	IV	192	11	5.7	No	[58]
Post-Kidney transplant	Corticosteroids	IV	386	9	2.3	No	[59]
Arthritis	Methotrexate	IV	70	2	2.9	No	[60]
Overall Phase IV			29,512	1,125	**3.8% (2.3-5.7%)**		

Table 2:

Variable of Interest	Pre-Clinical	Phase I	Phase II	Phase III	Phase IV	Reference
Model Inputs						
Number of Animals/Patients	800	80	100	1,000	10,000	9
Discount rate = 3.5%						10
Average branded price US$ 65.40						11
Expected yearly sales = 1,000,000 units						Model
Time for phase of the trial in years	3	1.8	2.1	2.5	2	9
Cost of cataracts surgery for both eyes (US$)	0	2,710	2,710	2,710	2,710	8
Initial nominal cost per animal/patient in trial (US$)	7,500	15,700	19,300	26,000	0	6,7
Control Parameters						
Probability of a favourable outcome (a)	0.4	0.15	0.32	0.26	0.1	Model
Probability of adverse event (i.e. cataract) *(b)*	0.1	0.05	0.02	0.02	0.01	Model
Treatment Parameters (Base case, no screening assay)						
Probability of a favourable outcome *(c)*	0.8	0.9	0.8	0.9	1.0	Model
Probability of adverse event (i.e. cataract) *(d)*	0.22	0.088	0.03	0.037	0.048	Model
Conditional probability of success in each stage of the trial (CP=c-a)	0.40	0.75	0.48	0.64	0.90	9
Conditional probability of cataract in each stage of the trial (CP=d-b)	0.12	0.038	0.01	0.017	0.038	Systematic review
Treatment Parameters (Screening Assay)						
Probability of a favourable outcome	0.8	0.9	0.8	0.9	1.0	Model
Probability of adverse event (i.e. cataract)	0.1	0.05	0.02	0.02	0.01	(Base equal to controls)

Table 3:

Base case scenario	Branded Price (US$)	Break-even time (Years)	Cost of trial (US$)
	30	1.08	32,378,611.66
	40	0.81	32,380,458.38
	50	0.65	32,380,064.45
	60	0.54	32,380,182.75
	70	0.46	32,380,427.01
	80	0.40	32,379,367.41
	90	0.36	32,380,891.32
Mean cost			32,380,000.43
Screening Assay	30	1.04	31,322,474.13
	40	0.78	31,322,964.69
	50	0.63	31,322,248.77
	60	0.52	31,322,645.77
	70	0.45	31,322,366.26
	80	0.39	31,322,744.66
	90	0.35	31,323,115.81
Mean cost			31,322,651.44
Difference in cost			1,057,348.99

N.B. Costs are calculate from the economic model and therefore vary slightly from one price point to the next