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Finding the Patients for Respiratory Clinical Trials; Successful Recruitment by Adapting Trial Design

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Abstract

There is increasing need to develop new therapeutics for respiratory diseases such as asthma and COPD, driven by the rising global prevalence, association with significant morbidity and mortality and limited current treatment options. However, recruitment of patients into respiratory trials remains challenging, time-consuming and often very costly. As a consequence, recruitment times frequently have to be extended during the trial to reach the recruitment goal. To identify key changes in trial design which could lead to improved recruitment in respiratory trials, trial recruitment between 1999 and 2012 was analyzed using data from Citeline Trialtrove. The manner by which trials met their recruitment goal was analyzed together with a more in-depth study of trials terminated due to poor recruitment. The percentage of respiratory trials found not to be recruiting to target was substantial (average 26.3%). Whilst no significant changes in recruitment to target were observed during the time period, there appeared to be a trend towards shorter recruitment times. Common features of poorly recruiting trials were very few centers and strict eligibility criteria. Recruitment is central to clinical trials and more complex trials enrolling more specific patient populations will prove increasingly challenging. Therefore, it is important to both consider by what means recruitment will be affected when making trial design decisions and to ensure that every eligibility criteria is as inclusive as possible while still maintaining selection of the right patient population.

Keywords: Recruitment; Clinical; Respiratory; Asthma; Chronic obstructive pulmonary disease

Abbreviations

RCT: Randomized Clinical Trials; UK: United Kingdom; COPD: Chronic Obstructive Pulmonary Disease; ICS: Inhaled Corticosteroids; LABA: Long-Acting Beta Agonist; EMA: European Medicines Agency; AZ: AstraZeneca; GSK: GlaxoSmithKline; P/C/M: Patients/Center/Month; UKCRC: United Kingdom Clinical Research Collaboration; ECRIN: European Clinical Research Infrastructures Network; HTA: Health Technology Assessment; EQ5D: EuroQol 5-Dimensions; WPAI: Work Productivity and Activity Impairment; HCRU: Health Care Resource Use

Introduction

Randomized controlled trials (RCTs) are considered the gold standard for assessing unbiased information about efficacy and safety of new drug candidates [1]. Several key features of RCT design and conduct are crucial to a successful and statistically valid outcome, including choosing the right patient population and appropriate endpoint(s), as well as ensuring appropriate recruitment and randomization into the study arms. Indeed, recruitment is commonly recognized as one of the big challenges in RCTs. A study of UK funded trials 2001-2005 revealed that less than one third recruited to target [2]. This brings about significant problems including inconclusive results, premature termination of trials and increased costs [3]. The difficulties in recruitment also lead to considerable delays in clinical programs; recruitment challenges have been reported to be the cause of 45% of study delays [4]. In an attempt to overcome these issues the recruitment time is often extended (56% of the time) and/or additional sites are added (44% of the time) [5]. However, inclusion of too many sites can lead to problems with validity of study outcomes as full consistency between centers is difficult to achieve [6]. Several reviews have identified possible causes of poor enrollment to mainly belong to three areas; trial design, organization and patient/physician barriers [7-9]. Each of these features is highly dependable upon the disease and therapeutic agent being explored. This paper describes some of the key challenges associated with trial design and recruitment into respiratory disease trials.

Challenges specific to respiratory trials (asthma and chronic obstructive pulmonary disease)

Respiratory diseases including asthma and chronic obstructive pulmonary disease (COPD) affect a large part of the population and each year great amounts of resources are spent to improve the quality of life for these patients. Despite the high unmet medical need, relatively few novel therapies have successfully entered the market during recent years, highlighting the challenges of drug development within this field [10]. Asthma now affects over 300 million people in the world, and its prevalence is rising, particularly in developing countries [11]. In the past asthma was seen as a disease of bronchoconstriction due to the release of bronchoconstrictor mediators from mast cells. More recently it has been viewed as a heterogeneous inflammatory disease of the airways, defined by the history of respiratory symptoms such as wheeze, shortness of breath,

chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation. Symptoms and airflow limitation may resolve spontaneously or in response to medication, and may sometimes be absent for weeks or months at a time. On the other hand, patients can experience episodic flare-ups (exacerbations) of asthma that may be life-threatening and carry a significant burden to patients and the community [12]. In contrast, COPD is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases [13]. Exacerbations and comorbidities also contribute to the overall severity in individual patients. COPD is now recognized as the fourth leading cause of death worldwide and results in an economic and social burden that is both substantial and increasing. For the EU, the annual costs of healthcare and lost productivity due to COPD were estimated as €48.4 billion and those due to asthma at €33.9 billion by the European Respiratory Society. Overall, the combined annual number of deaths in the EU due to asthma and COPD exceeds 150 thousand, clearly highlighting the need for therapies to treat these diseases [14].

There is pressing need to develop new therapeutics for asthma and COPD, driven by the rising global prevalence, association with significant morbidity and mortality and limited current treatment options. However, both asthma and COPD have several characteristics that pose challenges for drug development. Firstly, neither asthma or COPD are single diseases, rather they are increasingly recognized as heterogeneous in nature and characterized by several phenotypes [15]. Clinical development programs need to consider whether to target the whole spectrum of patients for the disease or only patients with one clearly defined entity of the disease, such as chronic bronchitis or emphysema within COPD. Secondly, given that drugs may be developed to improve differing aspects of the diseases (e.g. improve airflow obstruction, provide symptom relief, modify or prevent exacerbation, or alter the natural progression of the disease) studies can involve different endpoints, study designs and study duration. Therapeutic drugs that modify either the severity or duration of exacerbations or prevent exacerbation events will provide meaningful benefit to vast number of patients. As such, exacerbation rate is one of the most clinically relevant endpoints to assess symptom control and it is often required in Phase III studies for long term control medications [16]. However, exacerbations in both asthma and COPD are random and relatively rare events which make them complicated to use as an endpoint in a clinical study setting and traditionally result in large and lengthy studies.

In an attempt to overcome many of the challenges described above, respiratory RCTs are becoming increasingly sophisticated and complex in design. This is partly attributed to a more highly competitive space in drug development, as attention turns towards more specific patient sub-groups within these complicated chronic diseases. In the case of asthma, patients with severe disease account for a disproportionate amount of health care spending; they require hospitalization, use a lot of medications, and miss time from work. Additionally, as more companies are developing therapies in the same disease area a larger body of information is needed to distinguish a new product from those already on the market [17]. This is particularly apparent when aiming to improve on existing treatments, such as ICS and LABAs, the mainstay in asthma and COPD therapy [12,13]. As the quest to find new drugs against novel targets intensifies, so too does the need to clearly identify the specific phenotype/endotype of patients where the treatment will be deemed effective. Equally, it is increasingly recognized that different therapeutic approaches may have effects on different aspects of the inflammatory process in both diseases and so several outcome measures may be required in the clinical development of new treatments [18,19]. Taken together, these features are driving an unprecedented level of complexity in respiratory RCT study design which places additional stress on investigators and patients. This report describes how recruitment in asthma and COPD trials has changed over the last 15 years and discusses suggestions on how to improve recruitment by trial design.

Methods

Investigating recruitment in clinical trials

A search was performed in the Citeline database Trialtrove to investigate how recruitment has changed in asthma and COPD trials over the last 15 years. Citeline Trialtrove was chosen as a source because it provides a comprehensive collection of trial data including the timings needed for calculations of recruitment times and recruitment efficiency. The following search criteria were used. Asthma and COPD, Phase I/II II/III, Completed/Terminated, End dates from 01.01.2000 to 01.01.2015

The search generated n=2673 trials. Very few trials started during 2013-2014 had completed reporting, and therefore these years were excluded and the investigated time period was limited to trials started between 1999 and 2012. Out of the 2673 trials, n=742 (~30%) had start dates between 1999 and 2012 and provided information for target accrual, actual accrual, number of centers and actual enrollment duration. These 742 trials were assumed to provide a representative sample of all trials and their information was used to calculate patients/center/month and the percentage of trials that did not recruit to target for each year.

To find common features in trials with poor recruitment the following search criteria were entered in Trialtrove:

- Asthma and COPD
- Phase I/II II/III III
- Completed/terminated
- End dates from 01.01.2000 to 01.01.2015
- Terminated due to poor enrollment

This provided 12 trials that stated that their primary reason for termination was poor enrollment. Trials were compared to find common features.

Statistical analysis

Statistical analysis was performed by calculating the mean and 95% confidence interval (CI) using Graph Pad Prism 6 software. Statistical significance was evaluated by student's t-test and $p<0.05$ was considered significant

Method considerations

The method for investigating features of recruitment in asthma and COPD trials was based on the assumption that the trials that reported their target and actual accrual are not different from the ones that did not. There is a risk for biased information in the sense that trials with successful recruitment may be more likely to report it, hence there could be an underestimation of how many of the trials that are not recruiting to target. Also this data does not include considerations on whether actions were taken to increase recruitment, such as increasing

the recruitment time or number of sites. This definition of recruiting to target does not separate trials that had to extend recruitment time to reach target from those that did not. When investigating trials terminated as a result of poor enrollment it is important to consider that poor enrollment will bring other challenges to the trial that easily could have been named as the reason for termination instead of poor recruitment. For example, terminated due to lack of efficacy if results were not properly statistically powered and efficacy could not be proven. Consequently, the 12 trials cannot be assumed to represent all trials terminated due to recruitment problems. Rather, these trials represent interesting case studies where recruitment was reporting as the reason for termination of the trial.

Results

Respiratory trial recruitment trends during the last 15 years

For n=742 asthma and COPD trials started between 1999 and 2012 information about target and actual accrual was reported in Cite Line Trialtrove (Figure 1A). Of these, the percentage of trials not recruiting to target is presented in Figure 1B. There appears to be an increase in the number of respiratory trials over the period 1999-2012. This may be due to the fact that the proportion of trials reported in Trialtrove is increasing, however a surprisingly large part of trials generated in the search did not report actual start date. The percentage of trials failing to recruit their target sample size is considerable with numbers ranging from 14% to 40% and an average over the period of 26.3%. This suggests more than one out of four trials is not reaching the recruitment target and may consequently have issues with statistically valid outcomes.

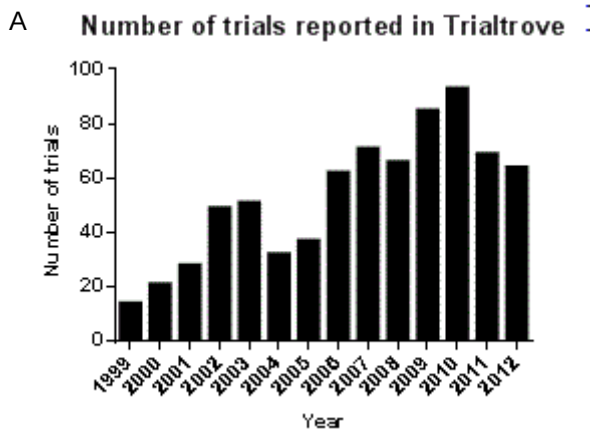

Figure 1A: Number of respiratory trials reported in Trialtrove from 1999 to 2012.

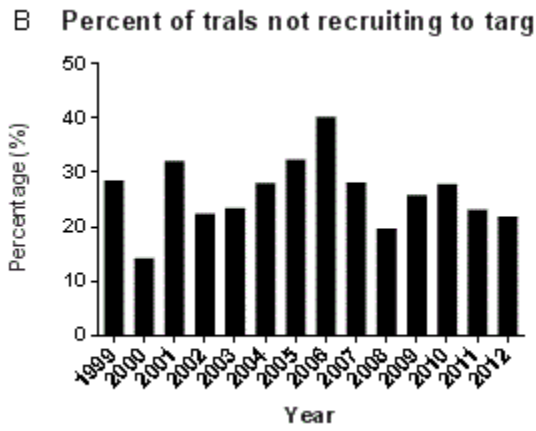

Figure 1B: Percentage of trials in asthma and COPD not recruiting to target. Poor recruitment is a major issue with an average of 26.3% of trials failing to recruit to target over the 1999-2012 period.

A comparison of the four major commercial sponsors of asthma and COPD trials, Boehringer, GlaxoSmithKlein (GSK), Novartis and AstraZeneca (AZ) showed that between 1999 and 2005 the average percent of trials not recruiting to target was 3.5% for Boerhinger, 21.02% for Novartis, 19.4% for GSK and 30.8% for AZ, which can be compared to 25.9% for all trials. During the second half of the investigated period, 2006 to 2012, the average percentage of trials not recruiting to target was 34.7% for Boehringer, 24.5% for Novartis, 23.2% for GSK, 12.0% for AZ and 26.7% for all trials (Figure 2 and Table 1). As shown, AZ showed a decrease in the average of Trialtrove reported respiratory trials not recruiting to target comparing 1999-2005 and 2006-2012. Part of the improvement in AZ sponsored trials could be ascribed to AZ having the highest percentage of trials not recruiting to target during the first half of the period. Boehringer appeared to have a major increase in Trialtrove reported respiratory trials not recruiting to target whilst Novartis and GSK had small changes. It should be kept in mind that for the current searches, Boehringer appeared to sponsor fewer trials than the other companies, specifically during the first part of the investigated period, making the comparison across time periods more uncertain.

Enrollment trends in respiratory trials

Patients per center per month (P/C/M) is a widely used measure to assess patient recruitment efficiency and we therefore next explored how this has altered during the 1999–2012 period. Mean P/C/M numbers for asthma and COPD trials from 1999 to 2012 are presented in Figure 3. As shown, there appears to have been an increase in P/C/M over the period, which is similar for both Phase II and Phase III studies. However, variability in P/C/M appears quite significant, especially during the most recent years which makes it difficult to assess the validity of any these observed changes in P/C/M.

	Trials from sponsor with required information 1999-2005	Trials from sponsor with required information 2005-2012	Total trials from sponsor with required information 1999-2012	Total respiratory trials reported from sponsor
Boehringer	19	49	68	140
Novartis	28	88	116	227
GSK	66	104	170	245
AZ	54	57	111	175
All trials	277	524	749	2673

Distribution of reported trials in Trialtrove over the four major sponsors in relation to all trials for the investigated 1999-2012 time period

Table 1: Number of trials reported in Citeline Trialtrove.

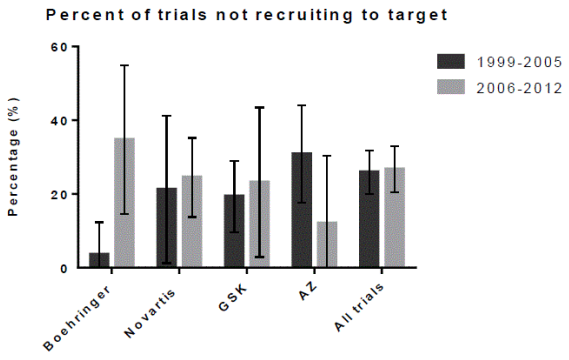

Figure 2: Mean percentage of trials not recruiting to target with 95% CI for four major sponsoring companies.

Given that P/C/M may be increasing, we next sought to find possible explanations. Extension of the enrollment duration has been identified as one of the most common measures to manage poor recruitment. Mean enrollment duration for asthma and COPD trials is presented in Figure 4. As shown, there appears to be a trend for shorter mean enrollment times over the entire 1999–2012. There is no apparent difference when comparing mean enrollment times for Phase II and Phase III studies. Consequently it can be argued that the trend for shorter mean enrollment duration is driving the increase in P/C/M.

The number of centers used within a clinical trial may also influence recruitment times. We next explored the mean number of centers used in each clinical trials investigating asthma and COPD. As shown in Figure 5, the number of centers used in these trials appears to have remained relatively stable over time and does not appear to have differed significantly for Phase II or Phase III studies. Hence, it is plausible that the trend for a decrease in enrollment times is not due to the employment of more centers but rather a more efficient recruitment.

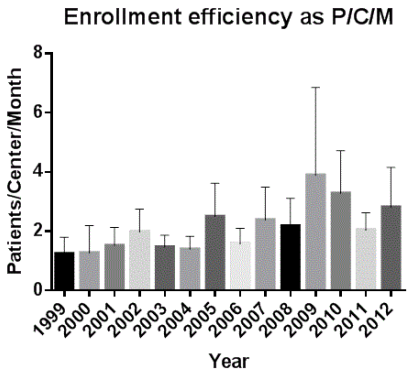

Figure 3: Mean number of patients/center/month (P/C/M) with 95% CI for each year between 1999 and 2012. There may be a trend for increasing P/C/M over the 1999- 2012 period.

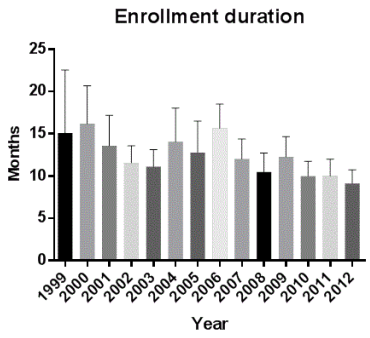

Figure 4: Mean enrolment duration in asthma and COPD trials from 1999 to 2012 with 95% CI. There appears to be a trend for decreased mean enrollment time over the 1999-2012 period.

A closer look at trials terminated due to poor enrollment during the last 15 years

During our Citeline Trialtrove search, twelve asthma and COPD trials were found to be tagged as "terminated due to poor enrollment" during the last 15 years. Whilst these trials cannot be assumed to represent all trials terminated due to recruitment problems for reasons discussed above, they represent interesting case studies where recruitment was reporting as the reason for termination of the trial. Relevant trial information is presented in Table 2 and common features were observed amongst them. Five trials had a very narrow patient population and/or constrained eligibility criteria (ID 153363, 061651, 081437, 049573, 061463). Three of these five had hospitalization after an acute exacerbation (or worsening in the case of COPD) as their eligibility criteria (ID 049573, 061651 and 061463) which certainly limits who can partake. In addition, it may be difficult to enroll patients who are under the stress of being in an emergency room with acute exacerbation. The two other identified trials investigated restricted patient groups; patients with pulmonary

hypertension (ID 153363) and patients with acute deconstructive heart failure with obstructive airways disease (ID 081437).

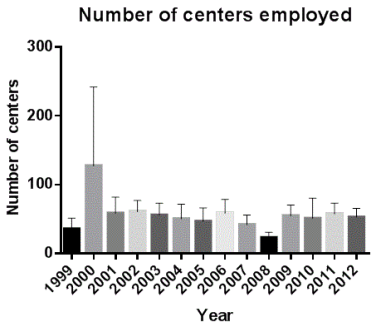

Figure 5: Mean number of centers employed in trials for each year between 1999 and 2012 with 95% CI. The average number of centers used for asthma and COPD trials have remained fairly stable over the 1999-2012 period.

Eight of the trials which were terminated due to poor enrollment appeared to only have recruitment at one center. One of these trials also reported problems with recruitment due to patients with desired profile already being treated with the investigated substance (ID 136694). All except one trial shared common features; one center or apparent narrow patient population/eligibility criteria. The only trial that did not fulfill any of these two criteria (ID 057796) performed better than the others in terms of recruiting its target number of patients (recruiting 79% of its target compared to 55% for the second best trial (ID 102676)). This trial stated that it was difficult to recruit patients with uncontrolled asthma despite regular treatment with inhaled corticosteroids [20], consequently the eligibility criteria may have been too strict.

Discussion

In the present work, we have identified the percentage of respiratory RCTs not recruiting to target to be in the range of 14% to 40% between 1999 and 2012. This is of concern considering the consequences of poor recruitment, including wasted time and money, but also compromised statistical validity of outcomes and ethical obligations to patients within the trial. When comparing the percentage of trials not recruiting to target between the four major sponsors and industry average we found evidence that trials sponsored by big pharmaceutical companies are in general better at recruiting to target. This is perhaps not surprising considering the difference in resource and operational capacity between large pharmaceutical companies and other sponsors such as, small biotechs and academic groups. Larger pharmaceutical companies may have more experience and data on how long it takes to recruit a specific study population which in turn makes initial goalsetting easier.

Trial Trove ID	Drug	Narrow patient population/ eligibility criteria	Only one center	Target accrual	Actual accrual	Accrual in percentage of target	Number of centers
153363	Iloprost trometamol	x	-	76	2	2,63	11
136694	Montelukast	-	x	50	1	2	1
105143	Lactic acid bacteria, VSL	-	x	20	3	15	1
102676	Bosentan	-	x	20	11	55	1
88269	AKL-1	-	x	164	33	20,1	1
105287	Prednisone	-	x	40		0	1
74150	Interferon		x	80	1	1,25	1
61651	Zileuton	x		520	119	22,9	19
81437	Nesiritide citrate	x	x	40	6	15	1
57796	Budesonide, formoterol	-	-	1000	791	79,1	52
49573	Budesonide, formoterol	x	-	600	41	6,83	20
61463	Salbutamol	x	x	340	42	12,4	1

Table 2: Relevant features of respiratory clinical trials terminated due to poor enrolment.

RCTs are becoming increasingly complex in terms of design, endpoints and statistical analysis [19]. For the respiratory field, this increased complexity is driven by several factors including the heterogeneous nature of asthma and COPD, and greater recognition that different therapeutic approaches may affect different aspects of the inflammatory process, thus requiring several outcomes to be measured within the trial. Inherently, increased trial complexity leads to the risk of reduced patient recruitment, particularly if trial design and required endpoints place additional stress on investigators and patients. Yet despite the increasing complexity, we observed a trend for shorter enrollment times in respiratory trials, suggesting that actions are being taken to improve recruitment. In this respect, it would be interesting to

identify the percentage of respiratory trials which extended recruitment times or added sites in an attempt to improve recruitment. Unfortunately, this information is not available in the Citeline database, however the publication by Bower and colleagues indicated that response to recruitment problems includes extending the recruitment period (56%); seeking additional funds (31%); introducing other recruitment methods (18%); increasing the number of sites (44%); recalculating power (21%) and finishing with insufficient patients (18%) [5]. Respiratory RCTs may already be relatively long given the endpoints which are commonly used and so the option to include additional centers may be preferable than extending recruitment time.

When discussing increasing complexity in trials it is important to acknowledge that some of this is driven by constraints of the health care industry. Beside the increasing demand from regulatory bodies, new stakeholders like payer/ Health Technology Assessment (HTA) bodies come with additional requirement of data to collect from the clinical trial. This new data includes measurements to support the value demonstration required for value development of the new technology to receive reimbursement and market access. However, the most important instruments used, (EuroQol 5-Dimensions (EQ5D), Work Productivity and Activity Impairment (WPAI), Health Care Resource Use (HCRU), and the data which is collected only increase time burden and complexity for patients and study centers to a small degree. A greater challenge comes likely from the need of including patients in the clinical program reflecting the right target patient population aligning requirements from science perspective, place in treatment algorithm, regulatory requirement, payer/HTA requirement. Targeting patients with a high unmet medical need increases the likelihood to receive a more favorable reimbursement and market access situation.

The Cochrane collaboration methods group published a comprehensive meta-analysis review of the design and conduct of RCTs [21]. Whilst not specific to respiratory trials, their findings share several similarities with our results, including the importance of not overestimating the expected recruitment rates and not having overly strict inclusion criteria. A more recent Cochrane review examined the effects of trial design change on recruitment [9]. Here, it was concluded that having an open design and active comparator rather than placebo had positive effects on the recruitment. However, the effects of eligibility constraints or number of sites involved were not discussed as part of this review. Both Cochrane reviews highlighted recruitment efficiency is affected by a large number of factors, therefore making it difficult to examine which are the key driving factors. However, given the accumulating amounts of recruitment data available from pharmaceutical companies and increased knowledge sharing, the use of modern technology to model recruitment should allow for better recruitment rate estimations in the future.

Increased awareness of recruitment issues and proactivity in finding solutions is essential. Several reviews have examined areas of issues associated with recruitment [7-9]. Of these, the area of trial design has been subject to the greatest amount of change during the last couple of years. This has been driven by new regulatory requirements requesting enhanced information for submissions, and increasing competition for market shares within the field. These changes have subsequently caused other issues within the two other areas such as increased workload for the physician and greater difficulties in organization of more complex clinical trials.In our review of trials terminated due to poor recruitment we identified emerging common features which warrant attention. Firstly, only employing one site, appears to hamper recruitment of the desired number of patients. Even if one site seems to have the capacity to recruit all the patients it may be worthwhile including two or three sites to spread and decrease risk. Secondly, targeting of a more specific patient population requires careful choice of investigators and sites to enable fulfillment of inclusion criteria and successful recruitment. It should be noted that this investigation has not examined regional variations in recruitment rates. Internal AZ experience has shown a wide variation in P/C/M from region to region, however it may come at a cost of quality. Further investigation in this area is required to better understand the drivers behind regional differences. Thirdly, the right inclusion and exclusion criteria is key for a successful trial. When drafting the criteria each point should be evaluated and challenged to assess whether it is as strict as needed and at the same time as including as possible. There is a careful balance between selecting for the right patient group in order to demonstrate efficacy, whilst maintaining an appropriately sized patient group in order to facilitate recruitment in a timely manner. Implementing techniques to evaluate the most favorable inclusion criteria could have a great impact on recruiting the right patients in a timely manner increasing cost efficiency and avoiding non-significant results for trials that have a true significance. In addition, it can be noted that several of the trials that were closed down due to poor recruitment had recruitment in admittance to hospital as an inclusion criteria, consequently patients were recruited upon arriving at the hospital or emergency room. This form of recruitment appears to be problematic, one possible reason for this could be that patients arriving at the hospital are less willing to go through the administrative parts of enrolling in a study whilst they are in need of immediate assistance with their illness. In an attempt to overcome challenges associated with inclusions/exclusions criteria, novel approaches for example using adaptive design to aid recruitment have been suggested. This may include adapting the eligibility criteria after interim analysis of the trial results to better suit the needs of the trial [22]. Unfortunately, choosing the right eligibility criteria to recruit the right population is more difficult without good knowledge of biomarkers. In diseases such as asthma and COPD, where biomarker knowledge is relatively low, the need for methods to choose the right eligibility criteria is even higher.

Conclusion

Whilst there appears to be no clear “quick fix” to improve recruitment in respiratory trials, several actions are emerging which could improve the process of recruiting the right patient within a reasonable time.

Choosing the right centers

Ensure other similar trials are not ongoing at the same time.

Utilize several centers with known large patient databases.

Select sites with proven track history of successful recruitment to target.

Choosing the right eligibility criteria

Challenge every inclusion and exclusion criteria to evaluate if it could be made more inclusive.

If previous trials or pilots have been run, make sure to evaluate screening failures and make appropriate adjustments to maximize recruitment and retention success.

Learning from previous experience

Establishing infrastructure to make sure that learnings from previous trials are captured and that mistakes are not repeated.

Reducing complexity

COPD and asthma trials are already complicated and it should be evaluated if the extra information gained from an additional test or process is actually needed or just nice to have.

Assess if any procedure could be simplified.

Reduce the recruitment hurdles for patients by applying the appropriate clinical operations logistics and technology.

Recruitment is central to the success of RCTs and it is crucial to consider the impact any study design decisions may have upon its efficiency. Implementing the above changes may provide a step towards streamlining the recruitment process, however continual evaluation of factors contributing to poor recruitment is required in order to address these challenges in future RCTs.

Transparency

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