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Seasonality: The Clinical Trial Manager's Logistical Challenge

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1. Introduction

Seasonal variation in the incidence of diseases has been observed for centuries, dating back at least to ancient Greece, and yet scientific understanding of its underlying mechanisms remains relatively rudimentary for many diseases.[1] Seasonality is not only an important factor in common infectious diseases (such as influenza, chickenpox and measles) but also in non-infectious diseases such as seasonal affective disorder (SAD) and rheumatoid arthritis (RA). The complexity of seasonality of both infectious and non-infectious diseases – incorporating as it does the diverse disciplines of epidemiology, pathology, immunology, meteorology, population dynamics and statistics – has resulted in few coherent hypotheses that satisfactorily combine each contributing factor.[2] There are plenty of plausible qualitative theories surrounding disease seasonality, but, with a few exceptions, supportive quantitative evidence is somewhat lacking.

Clinical development is, at the best of times, a complex, long, frustrating process in an ever changing regulatory environment. It is akin to working hard for up to 10 years to answer one question, only to realise that in the meantime the question itself has changed. In the sometimes futile attempt to ensure the timely delivery of patient data to the regulators, the management of clinical research involves a great degree of planning, organising and execution by highly qualified and professional personnel, as well as involving some elements of chance. The clinical trial managers who are bestowed with this unenviable task are faced with considerable logistical decisions and the need for significant depth of knowledge, including but certainly not limited to: planning timelines, projecting budgets and managing budgets, whilst at the same time ensuring the delivery of a high quality product. However, management for seasonal diseases adds to this complexity, regarding fluctuations in the incidence of the disease studied; the recruitment of patients to coincide with a particular part of the year (dependent on latitude, of course) and the attentiveness to unexpected changes in the pattern of the disease and their implication on the running of the clinical trial.

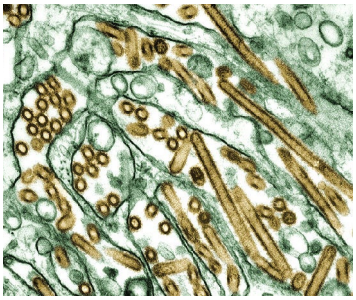
Mathematical modelling has provided the advancement necessary to take the hypotheses of seasonality and apply them to the field. Nevertheless, given the complexity of seasonality, a serious limiting factor to quantitative analyses and predictive models of disease patterns is the lack of long-term disease records with similar data collected over a network of spatial locations.[3]

It is therefore the aim of this paper to discuss the multitude of complexities associated with running a clinical trial for a seasonal disease, and to suggest potential strategies as well as further research necessary to improve the execution of such trials, in order for the control and quality seen in less complex trial management to be transferred to the ever variable field of seasonal diseases. Firstly, a range of both infectious and non-infectious diseases whose incidences are affected by changes in seasonality (some more predictable than others) are discussed. There is then a discussion of regional fluctuation in influenza incidence, as an example of a seasonal disease. Finally, this knowledge is applied to the management of seasonal clinical trials.

2. Seasonal Disease Profiles

In this section five seasonal diseases are discussed (influenza, seasonal allergic rhinitis [SAR], seasonal affective disorder [SAD], rheumatoid arthritis [RA] and malaria). Each of these indications are seasonal in different ways. These brief overviews by no means present an exhaustive resource, but simply aim to highlight the varied driving forces behind seasonality of infectious and non-infectious diseases. Please see Table 1 for a more extensive list of seasonal diseases.

2.1 Influenza



Influenza ("flu"), an acute viral respiratory disease, is probably the seasonal disease that immediately comes to mind, and is perhaps of the most profound interest, as it is responsible

for much of the seasonal variation in other infectious and non-infectious causes of morbidity and mortality.[1] In 2008 alone there were 70611 cases of seasonal influenza (influenza A and B) worldwide, with the highest incidence being in the United States (41,106 cases).[4] In temperate regions, incidence of infections are characterised by flu seasons, generally exhibiting a marked increase during the winter months, with tropical regions showing a much less defined pattern.

Factors contributing to the seasonality of influenza can be divided into four categories:

- *Pathogen survival*: ambient temperature, relative humidity, vapour pressure
- *Pathogen evolution*: antigenic drift (rapid mutation), antigenic shift (re-assortment of genome)
- *Host resistance to infection*: melatonin and vitamin D levels (fluctuate with light/dark cycles)
- *Host behaviour*: amount of time spent indoors, aggregation of people

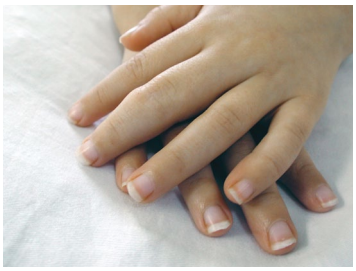
2.2 Allergic Rhinitis

Allergic rhinitis (AR) is a heterogeneous disorder that despite its high prevalence is often undiagnosed. It is characterised by one or more symptoms including sneezing, itching, nasal congestion and rhinorrhea. Many causative agents have been linked to AR including pollens, molds, dust mites and animal dander. Seasonal allergic rhinitis (SAR) is fairly easy to identify because of the rapid and reproducible onset and offset of symptoms in association with pollen exposure[5], as well as other allergens such as ragweed and fungus. In SAR, with relevant allergen sensitisation, the link between the seasonal allergen exposure and rhinitis is clear cut.[6]

2.3 Seasonal Affective Disorder

Seasonal affective disorder is a form of depression that tends to occur as the days grow shorter during the autumn and winter (this is known as winter SAD). Rates of winter SAD have been found to be significantly higher at the more northern latitudes.[7] As for allergic rhinitis, the direct link between SAD incidence and seasons is also evident: as the days grow shorter, daylight hours decrease. In fact, treatment for SAD often involves using artificial light as a supplement for the reduced daylight hours. In tropical regions winter SAD is very rare, if not non-existent although there are potential cases of summer SAD (depression as a result of extreme summer conditions) reported.[8]

2.4 Rheumatoid Arthritis



Rheumatoid arthritis, a chronic autoimmune disease that is characterised by pain, stiffness, inflammation, swelling and sometimes destruction of joints, is more often known by its sufferers as a seasonal disease than the general public. The weather and seasonal changes are often suggested by patients as causes for changes in joint related symptoms.[9] Results from scientific studies however, show discrepancies, with some indicating that the winter months cause more severe symptoms[9,10,11] and some indicating that the spring months cause more severe symptoms.[9] Others reported that the increase in absolute humidity in summer is unfavourable to symptoms and disease activity, but that due to less clothing and air conditioning, there is lower vapour pressure on the skin, allowing for a better outcome for RA symptoms.[12] There are also indications that less exposure to light during the winter months (causing pro-inflammatory cytokine and Vitamin D changes) may be the cause of RA symptom exacerbation.[9] However, there is a general consensus that RA symptoms worsen during the wet and/or cold months.

2.5 Malaria

Malaria is an acute or chronic disease caused by the presence of sporozoan parasites of the genus *Plasmodium* in the red blood cells, transmitted from an in-

fected to an uninfected individual by the bite of *Anophelese* mosquitoes, and characterised by periodic attacks of chills and fever that coincide with mass destruction of blood cells and the release of toxic substances by the parasite at the end of each reproductive cycle. With malaria, it is not necessarily the symptoms of disease that are seasonal, but the timing and the length of the transmission period. In this case, it is the action taken to prevent the transmission of the disease by the vector that is seasonal, and must coincide with the transmission period. Correlations of fluctuations in malaria rates with rainfall and river level in relation to the periodic availability of breeding habitats for the malaria vector have been observed. Peaks in biting densities correlated well with periods of (i) high water level in the long rainy season, (ii) low water level in the long dry season, and (iii) abundant rainfall in the short rainy season.[13] Minimum temperature, irrigation and sea surface temperatures (such as the El Niño Southern Oscillation) also show significant correlations with malaria incidence.[14],[15]

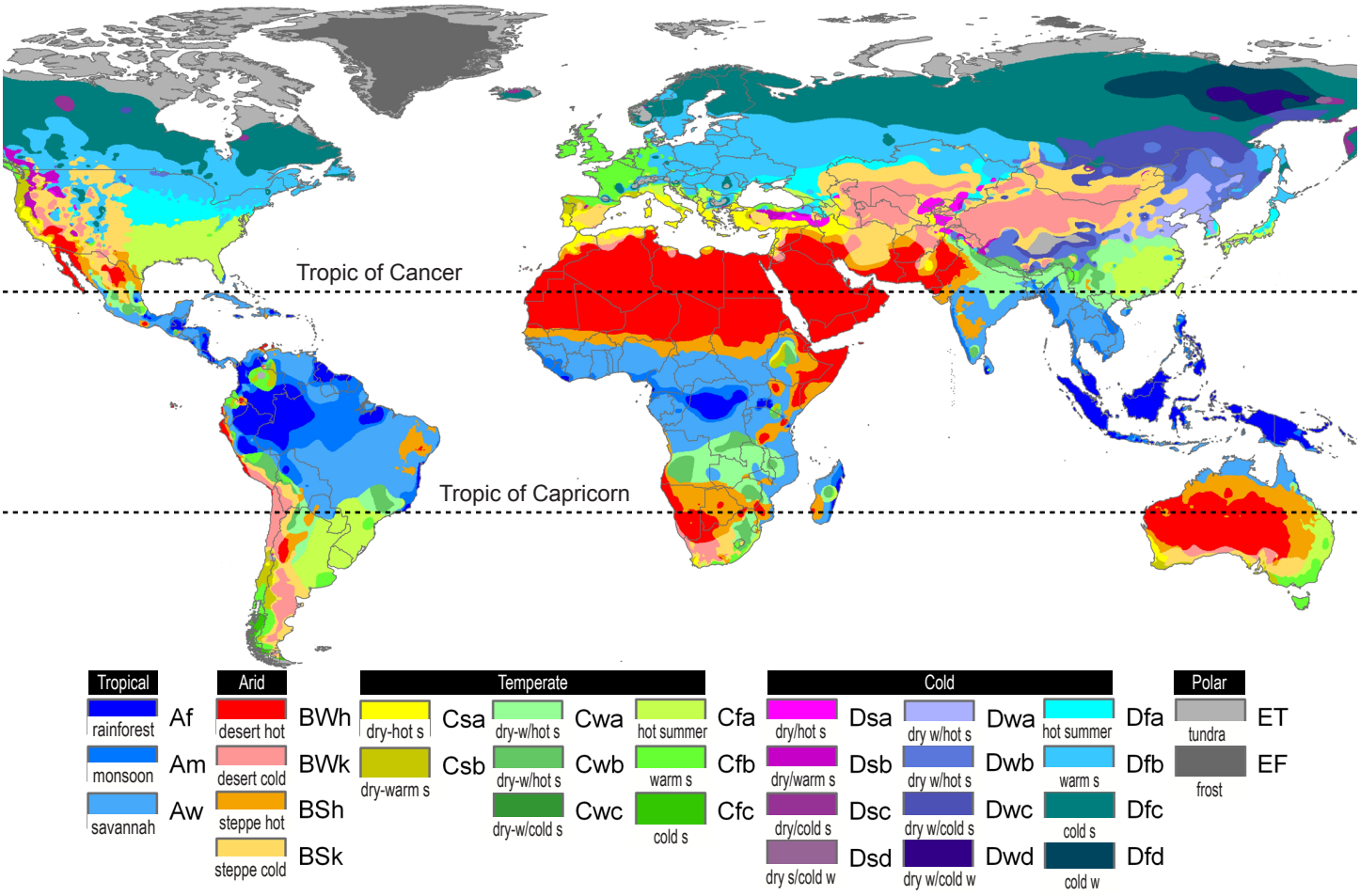
3. Regional Profiles

Standard geography subdivides the earth into regions by latitude: the northern temperate regions (north of the Tropic of Cancer), the southern temperate regions (south of the Tropic of Capricorn) and the tropical regions (between the Tropic of Capricorn and the Tropic of Cancer). The reason for looking at this division in this article is that the majority of seasonal diseases are affected by climate and temperature, which are largely an effect of a country's position in relation to the sun as a result of the tilt of the earth's axis. Besides the effects of solar radiation and its variations, climate is also influenced by secondary influences, including position relative to land and water masses, altitude, topography, prevailing winds, ocean currents, and prevalence of cyclonic storms.[16]

A map of the world indicating these differences in climate in Illustration 1[17], presented below.

One example of the difference in seasonal disease fluctuations between these regions is displayed in

World Map of Köppen-Geiger Climate Classification



the figures below. Data for seasonal influenza (A and B) detection was taken from the World Health Organisation (WHO) FluNet site, which collates global influenza data for the purpose of disease information and forecasting.

Figures 1 and 2 show the total incidence of influenza in 2008 and 2007, respectively. In 2008, the seasonality of the disease in the northern hemisphere is evident, with peak incidence during the winter months, low incidence during the spring and summer months, and a rise in incidence again at the beginning of winter. To a certain extent, the 2007 figures show a similar pattern, but it must be noted that the total number of data points for 2008 were 2283, and for 2007 were only 390 (earlier years have even fewer data points). This highlights further the lack of robust, easily-accessible historical data for seasonal diseases.

Looking at the 2008 data, the fluctuations in the southern hemisphere and tropics are less evident, perhaps partly due to the lower population in the southern hemisphere[18] and partly due to the fact that fewer data were available for these regions. However, when displayed individually (Figures 3 and 4) it is evident that the fluctuations in the southern hemisphere are a mirror image of those in the northern hemisphere, with peaks and troughs corresponding to the same seasons. Little fluctuation in incidence is seen in the tropics, where seasons are much less pronounced, if not totally absent.

Figure 1

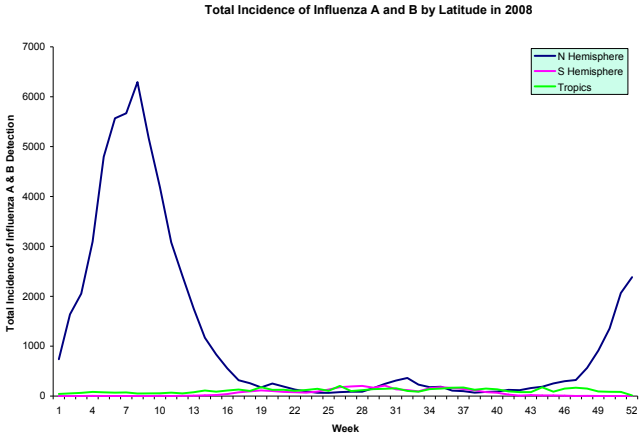


Figure 2

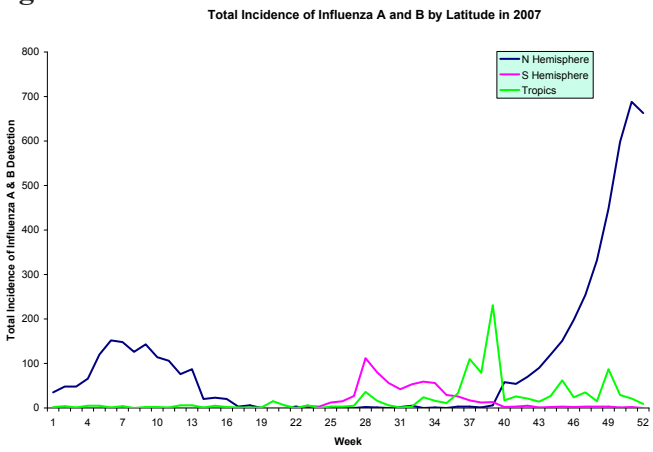


Figure 3

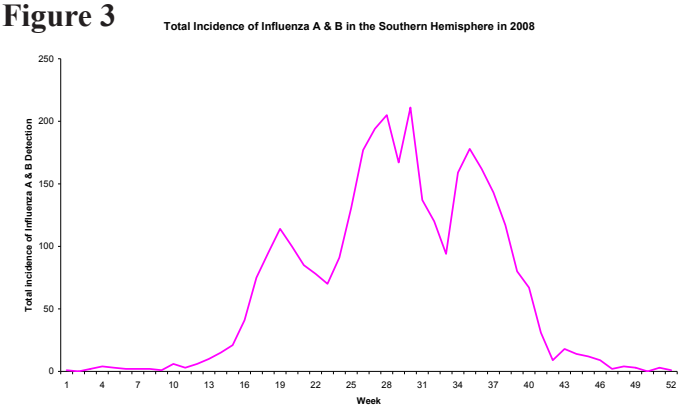
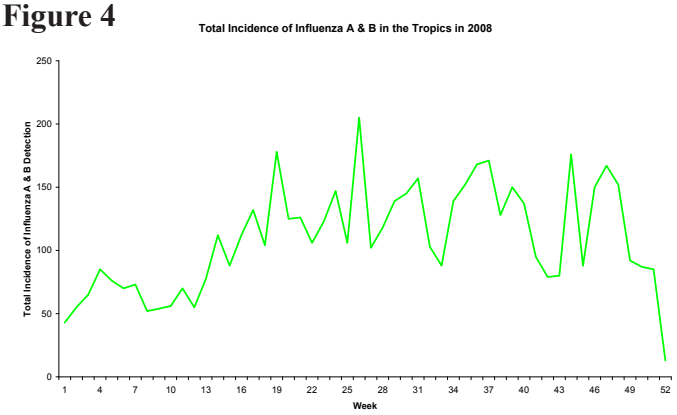


Figure 4



4. Incorporating Seasonality in Clinical Trial Management

4.1 Study Plan and Timeline Flexibility

It is evident from the data and information presented that the planning and management of timelines are going to be key to successfully running a seasonal clinical trial. From drafting the study design, through document submissions and patient recruitment, to the conducting of the trial itself, great care must be taken in the planning and meeting of timelines. Teams employed must be focussed, efficient, and resourceful, as

well as fully trained in the indication studied and its seasonality.

This section focuses largely on the discussion of infectious diseases. Ultimately, non-infectious diseases, such as seasonal allergies, are much more predictable, and the principles discussed below can be easily applied. However, the challenges really arise when dealing with infectious diseases, where seasonality can be much more volatile, and where clinical trial management must be at the same time both robust and flexible.

4.1.1 Patient Recruitment, Study Planning and Timelines

It is common knowledge that almost 50% of delays in clinical trials are a result of problems with patient recruitment.[19] Naturally, patient recruitment for a seasonal clinical trial needs to be completed before the studied indication reaches its peak incidence, and perhaps even before the increase in incidence begins (e.g. for indications with short seasons), if the study is to be carried out over the duration of the season. This alone raises issues: if one is recruiting patients for a seasonal indication, before that indication is evident, how can a site determine whether a patient *will* meet the inclusion criteria? For some indications, such as SAR, inclusion could perhaps be based upon the patient's medical records, but for an indication such as influenza, there is no way of knowing who will contract the virus. In these cases, there perhaps needs to be a rapid recruitment programme in place, to enrol patients as soon as the disease is diagnosed. It would also be wise to select sites with the capabilities to recruit larger numbers of patients within short timeframes. Conducting detailed feasibility for such diseases requires a thorough review of the incidence of the disease in previous seasons, and an assessment of the factors that influenced its incidence (e.g. particularly low winter temperatures). It is also of utmost importance to submit the trial to additional countries, as a delay of one month in obtaining regulatory approval in a single country could potentially set the trial back by six months. The 'luxury' of extending the patient recruitment period for this type of trial is simply not available.

Study design planning, protocol writing, site selection and investigator training to name a few need thorough attention regarding indication awareness, project management and time management. In particular, the following should be noted:

- It is paramount to know the peak incidence and peak timing of the indication in different countries/regions as this may vary considerably within a continent and/or hemisphere.
- The choice of participating countries/regions should be carefully selected so that regions with different timings of peak incidences and with a high probability of meeting the expected timelines can be included.
- The start-up should be carried out in phases (i.e. not all regions at the same time). The aim would be to activate and give priority to those regions which have the seasonal peak sooner and direct all resources towards that region/country, followed by those regions with a later peak. This must involve careful project management because the regions to be coordinated will be in different phases: some of them in start-up, some recruiting, and some with recruitment almost exhausted.
- Contingency plans should be put in place, taking into account that if at the beginning of the study the estimated predictions are not met, contingency plans are available that offer other regions for recruitment and options of different seasonal peaks – occurring later or lasting longer. The opposite situation may also occur, though less often: if recruitment expectations at the first sites initiated are exceeded and global recruitment is therefore able to end sooner than expected, additional resources/budget may have been wasted on open countries/sites with different seasonal peaks that will not ultimately be opened.

4.1.2 Document Submissions

With patient recruitment timing being such a key factor, it will be essential to submit clinical trial documents to the Ethics Committee (EC)/Competent Authority (CA) in good time, in order to receive approval of a trial before the planned start of patient recruitment. Certainly in the northern hemisphere, EC/CA members, investigators and patients tend to be on vacation during the summer months, and clinical trial approvals (as well as investigator contract approvals

and patient recruitment) are therefore delayed over this time. Submissions must be timed in coordination with the EC/CAs, even if it means early submission in order to guarantee trial setup timelines are met.

4.2 Mathematical Modelling of Seasonal Diseases

Mathematical models of infectious diseases have contributed significantly to scientific understanding of the dynamics of epidemics as they spread through large populations.[20]

The traditional model used is the SIR (susceptible-infected-resistant) model.[21] This model comprises Susceptible individuals (S), Infected individuals (I), and Removed individuals (R). Each individual begins in the susceptible class S, only to move to the infected class I after coming into contact with an infected person. Infected individuals eventually recover from the disease and then move on to the recovered class R. Being "recovered" and unable to be infected once again, they are essentially removed from the population and play no further role in the dynamics. Epidemics are continuously fuelled by the constant supply of new susceptibles that arise due to the birth of new individuals.[20]

Essentially the SIR model is relatively basic, and does not necessarily account for the numerous factors discussed in Section 2. More recently, these additional factors have been incorporated, including seasonality and "skipping dynamics", the principles of which yield promising forecasting tools[20,22], that have the potential to be used for managing seasonal trials.

Naturally, any mathematical model has its downfalls, as nature is never entirely predictable, even if incorporating so-called "chaos" factors. Ultimately, for one particular season, the model may be way off mark, and trial start-up and progress based on such a model would be thrown out of sync with the disease incidence.

4.3 Communicable disease surveillance programmes

Throughout the world there are in place a multitude of communicable disease surveillance programmes, coordinated by bodies such as the WHO, the Health Protection Agency (HPA) and the Centers for Disease Control and Prevention (CDC). Communicable disease surveillance is the continuous monitoring of the frequency and the distribution of disease, and death, due to infections that can be transmitted from human to human or from animals, food, water or the environment to humans, and the monitoring of risk factors for those infections. Significantly, an important part of communicable disease surveillance is also to detect the occurrence of outbreaks or epidemics so that immediate action can be taken to identify and control the source (e.g. outbreaks of food poisoning) or so that the health service is prepared to deal with increased numbers of patients (e.g. in a flu epidemic). [23]

It is of great importance, therefore, that when managing a seasonal study, good communication is maintained with the local, national and international surveillance networks, preventing study start up being initiated at any time other than within the ideal window of disease incidence.

Mathematical modelling and disease surveillance are intricately linked in the monitoring and control of communicable diseases, and it would be a serious omission on the clinical trial manager's behalf if these vast resources were not utilised in the planning and conduct of a seasonal clinical trial.

4.4 Resourcing

Having discussed the planning, monitoring and flexible time management needed to support a seasonal clinical trial, it is of no surprise that the teams involved need to be fully resourced, they need to be efficient and they need to have access to a whole host of information, including disease surveillance networks. Resourcing is one of the greatest challenges in the execution of these trials: it is not unfeasible to complete these trials much earlier than planned, much later than planned, or in a different region to that originally planned – all need thorough and comprehensive resource planning.

Choosing such teams, including suitable vendors of the highest quality, is no easy task, and must not be taken lightly. However, efforts invested at this early stage will undoubtedly pay off further down the line.

5. Conclusion: feasibility, Financial Costs and Rewards

Conducting seasonal clinical trials is certainly complex, involving intricate time management and disease forecasting requirements. Full planning is paramount,

and it has been seen that flexible patient recruitment, site selection and document submission plans are necessary for success. Having discussed the intricacies of seasonal clinical trial management, the question that will arise in any discerning manager's mind is whether such complex studies are financially viable; whether the initial investment pays off in terms of overall profit.

Certainly, there are significant opportunities (both in terms of public health and financial gain) in conducting seasonal clinical trials, and there is undoubtedly a gap in the market for such studies. However, detailed research must be carried out in order to forecast the necessary expenditure, potential profit and ultimate feasibility of conducting such trials.

Nevertheless, with the long term in mind, quality work for the most part does pay off. Having conducted a successful seasonal clinical trial the profile of the managing organisation will surely be greatly improved; respect among the industry will be enhanced; and subsequently overall profitability should in the fullness of time see a marked increase.

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Table 1 – A Collection of Seasonal Diseases

Sources: POI country questionnaires and Medline Plus, http://www2.merriam-webster.com/cgi-bin/mwmednlm (accessed 01 June, 2009)

Common/clinically important seasonal indications	Description	Climate required to initiate peak	Other factors influencing peaks
Allergic keratoconjunctivitis	Combined inflammation of the cornea and conjunctiva, caused by allergens	Warm/humid	Fungus spores, increase in pollen count, dust, animal hair
Allergic rhinitis	Inflammation of the mucous membrane of the nose marked especially by rhinorrhea, nasal congestion and itching, and sneezing caused by exposure to an allergen	Warm spring	High/increase in pollen count, pollution, pollen species involved
Asthma	A chronic lung disorder that is marked by recurring episodes of airway obstruction (as from bronchospasm) that is triggered by hyperreactivity to various stimuli (as allergens or rapid change in air temperature)	Warm conditions	Increase in pollen count, chemical substances, medicines
Atopic dermatitis	Inflammation of the skin characterised by symptoms (as asthma, hay fever, or hives) produced upon exposure, especially by inhalation to the exciting environmental antigen	Hot climate	Superheating, hyperhidrosis
Common cold (paediatrics)	An acute contagious disease of the upper respiratory tract and is caused by any of several viruses (as a rhinovirus or an adenovirus)	Cold weather, moisture	Society
Coronary heart disease	A condition especially caused by atherosclerosis that reduces the blood flow through the coronary arteries to the heart muscle and typically results in chest pain or heart damage	Winter	Cold weather exposure
Crohn's disease	Chronic ileitis that typically involves the distal portion of the ileum, often spreads to the colon, and is characterized by diarrhoea, cramping, and loss of appetite and weight with local abscesses and scarring	Early spring, autumn	Personal stress
Degenerative arthropathy	Degenerative disease of a joint	Spring and autumn	High humidity
Dengue hemorrhagic fever	Dengue (an acute infectious disease that is caused by a single-stranded RNA virus of the genus Flavivirus transmitted by mosquitoes of the genus Aedes) marked by hemorrhagic symptoms (as hemorrhagic lesions of the skin, thrombocytopenia, and reduction in the fluid part of the blood)	Rainy weather	Sanitary conditions for storing water
Depression	A state of being depressed as a state of feeling sad or a psychoneurotic or psychotic disorder marked especially by sadness, inactivity, difficulty with thinking and concentration, a significant increase or decrease in appetite and time spent sleeping, feelings of dejection and hopelessness, and sometimes suicidal thoughts or an attempt to commit suicide	Absence of sunshine	Winter blues
Epidemic encephalitis (tick)	Inflammation of the brain usually caused by a virus	Warm dry weather	Location, vaccination
Gout	A metabolic disease marked by a painful inflammation of the joints, deposits of urates in and around the joints, and usually an excessive amount of uric acid in the blood	Winter	Low temperature
Influenza	Any of several acute highly contagious respiratory diseases caused by strains of three major orthomyxoviruses	Cold weather, low temperatures / low humidity	High population density, health status (risk groups) , immunity, vaccination
Lupus Erithematosus	A disorder characterised by skin inflammation	Summer	Hot weather, sun
Lyme borreliosis	An acute inflammatory disease that is usually characterised initially by the skin lesion erythema migrans and by fatigue, fever, and chills that is caused by a spirochete of the genus Borrelia (B. burgdorferi) transmitted by the bite of a tick especially of the genus Ixodes	Warm dry weather	Location

Common/clinically important seasonal indications	Description	Climate required to initiate peak	Other factors influencing peaks
Malaria	An acute or chronic disease caused by the presence of sporozoan parasites of the genus Plasmodium in the red blood cells, transmitted from an infected to an uninfected individual by the bite of anopheline mosquitoes, and characterised by periodic attacks of chills and fever that coincide with mass destruction of blood cells and the release of toxic substances by the parasite at the end of each reproductive cycle	Monsoon	Warm humid weather and stagnant water
Measles	An acute contagious disease that is caused by a paramyxovirus of the genus Morbillivirus (species Measles virus); any of various eruptive diseases (as German measles)	Spring	Infection, contact with children
Pneumonia	A disease of the lungs that is characterised especially by inflammation and consolidation of lung tissue followed by resolution, is accompanied by fever, chills, cough, and difficulty in breathing, and is caused chiefly by infection	Winter	Cold weather, pollution
Psoriasis	A chronic skin disease characterised by circumscribed red patches covered with white scales	Summer	Hot weather, sun
Salmonellosis	Infection with or disease caused by bacteria of the genus Salmonella typically marked by gastroenteritis but often complicated by septicemia, meningitis, endocarditis, and various focal lesions (as in the kidneys)	Hot climate	Lack of adequate sanitary conditions for food
Seasonal affective disorder	Depression that tends to recur as the days grow shorter during the fall and winter	Winter	Reduced sunlight
Sinusitis	Inflammation of a sinus of the skull	Warm spring / summer months Cold winter months	Increase in pollen count Concomitant infections
Thyroid gland diseases	Diseases of, relating to, affecting, or being the thyroid gland	Summer	Hot weather, sun
Tuberculosis	A usually chronic highly variable disease that is usually caused by a bacterium of the genus Mycobacterium (M. tuberculosis), is usually communicated by inhalation of the airborne causative agent, affects especially the lungs but may spread to other areas (as the kidney or spinal column) from local lesions or by way of the lymph or blood vessels, and is characterised by fever, cough, difficulty in breathing, inflammatory infiltrations, formation of tubercles, caseation, pleural effusion, and fibrosis	Summer	Contamination of drinking water and airborne vectors
Viral Hepatitis E	A hepatitis that is common in some developing countries, usually contracted from sewage-contaminated water, and is caused by a highly variable single-stranded RNA virus (species Hepatitis E virus) of uncertain taxonomic affinities but related to members of the family Caliciviridae	Summer	Sewage as a source of contamination of drinking water

Patient Enrollment Experts Across Emerging and Traditional Markets

Rhinoconjunctivitis (Grass Allergy)

The sponsor of an allergic rhinoconjunctivitis study selected Pharm-Olam and another CRO (global company) for this competitive enrollment study.

Pharm-Olam delivered 235 or 65% out of the actual 362 randomized patients, despite the fact that the other CRO had 50% more sites and several weeks longer to recruit patients.

Country	Sites	Enrollment Period	Total Patients	Patients per Week
Pharm-Olam Poland	10	4 weeks	64	1.60
Pharm-Olam Germany	11	5.5 weeks	171	2.83
Other CRO in France, Italy, UK, Belgium, Netherlands	31	over 7 weeks	127	Less than 0.59

Seasonal Rhinitis

"By the end of the study Pharm-Olam was the highest recruiter with 263 randomized patients. In fact, out of 15 countries participating in the study, Pharm-Olam recruited almost 30% of all patients. The patient data collected from Pharm-Olam sites was of high quality with less than 2 queries per randomized patient.

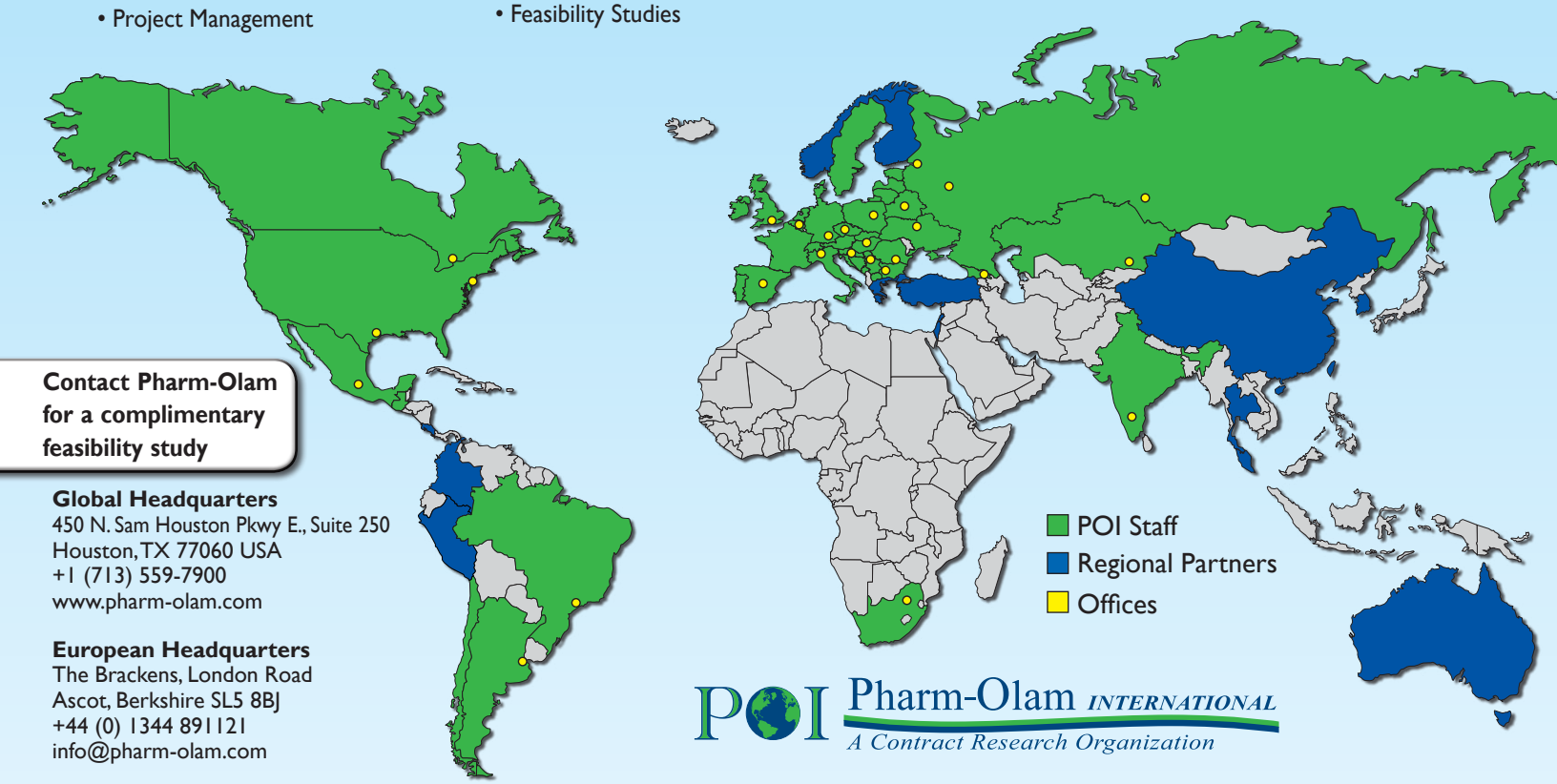
The recruitment was made respecting the set timelines at an appropriate speed. The team at Pharm-Olam, and their standards were well adapted to our working relationship. Communication between Pharm-Olam and us was good, and they are showing good reactivity to emitted requests.

The work performed by Pharm-Olam was kept within the study budget and their experience with Ethics Committees/Health Board was helpful in obtaining agreements from ECs. In conclusion, Pharm-Olam International gave us entire satisfaction." Reference Letter from Sponsor Study Manager.

Data from study was later used to support successful US NDA approval in pediatric indication

Comprehensive Services and Multi-National Coverage

- Rapid Patient Recruitment
- Monitoring
- Regulatory/Ethics Submissions
- Data Management
- Biostatistics
- Project Management
- Pharmacovigilance
- Import/Export Licenses
- Contract Negotiation and Administration
- Product Registration
- Feasibility Studies
- Protocol Design
- Health Outcomes Research
- DSMB Preparation
- Quality Control/Assurance
- Medical Writing
- CTMS
- Translations
- Registry Studies
- Investigator Meetings & Training



Contact Pharm-Olam for a complimentary feasibility study

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