WHITE PAPER

Economic Transformation Program (ETP) Entry Point Project (EPP) 2

Healthcare - Clinical Research

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Background

The Economic Transformation Program (ETP) was first presented to the public of Malaysia on 21 September 2010. Kick starting the programme will be 131 entry point projects (EPP) and 60 business opportunities, spread across 12 National Key Economic Areas (NKEA). The ETP is forecasted to create an incremental 3.3 million jobs, of which 63 per cent will be in the middle- and high-income segment.

Clinical Research has been identified as one of the ***six Entry Point Projects (EPP)*** under the Healthcare NKEA (EPP2). Under this EPP, it is the aim of the government to promote clinical research in Malaysia and increase the number of clinical trials conducted annually in Malaysia from the current figure of approximately 150 clinical trials per year to **at least 1000 new and ongoing clinical trials by the year 2020**. It is anticipated that such targets will generate a total revenue of US136.6 million.

It is important to acknowledge the vital role of Industry players (e.g. Multinational Pharmaceutical Companies, Contract Research Organizations), in ensuring the success of the EPPs. As the primary stakeholder, Pharmaceutical Companies are ultimately the sponsors for global or locally initiated clinical research projects. As such the decision making responsibility on allocation and placement of clinical trials resides with the respective Pharmaceutical Companies.

Meeting the targets set under this EPP, though highly challenging, is certainly achievable. In order to do so, it is highly critical that we make a concerted effort to identify existing gaps, acknowledge them and channel our resources and effort to plan and implement improvement measures in a timely manner.

In an increasingly competitive global environment, the importance of the partnership between Clinical Research Malaysia (CRM) and industry stakeholders must be recognized and acknowledged. Without a doubt, Pharmaceutical Companies are increasingly channeling their resources and bringing significant volume of clinical trials to Asia. Malaysia unfortunately, is not receiving an equitable share of the clinical trial pie as evidenced from current data (Fig 1) and hence not in the position to capitalize on the opportunities presented.

Urgent action is required to positively re-shape the research environment. Quick, effective and efficient implementation of identified solutions is necessary to support these goals.

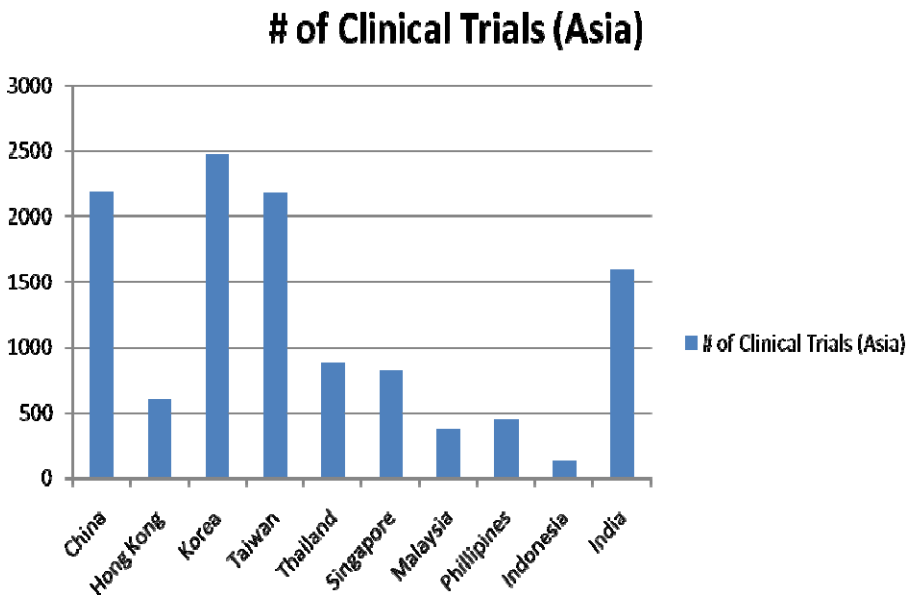

Fig 1 : Comparison of Clinical Trial Allocation in key Asian Countries , taken from Clinicaltrials.gov – May 2011

Objectives

The objectives of this White Paper are to seek the following:

1) Highlight the key areas of opportunities to drive research growth, reveal identified needs and actions to achieve the targets, from the perspective of key pharmaceutical industry stakeholders
2) Emphasize the importance of the collaboration of Industry players (including PHAMA) and CRM in this EPP initiative, to ensure prompt and effective implementation of the identified solutions

Current Status

There has been concerted effort over the years to shape the Clinical Research environment in Malaysia. The key stakeholders within the pharmaceutical industry have worked through PhAMA (Pharmaceutical Association of Malaysia) to drive positive changes and to grow the clinical research industry.

Noteworthy evolution and key milestones included:

- Formation of the National Clinical Research Committee (NCRC) in 1997
- Development of 1st Malaysia Good Clinical Practice (GCP) guidelines in 1999
- Defined regulatory (Clinical Trial Import License) processes, improved practicality and alignment with ICH requirements; Formation of dedicated Clinical Trial Unit
- Improved regulatory and Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review/approval timelines and meetings frequency
- Increased number of Clinical Research Centres (CRCs)
- Improved research facilities at certain sites

- Expansion in the pool of skilled Clinical Research Personnel (Study coordinators, Clinical Research Associates [CRAs], etc)
- Greater focus on GCP training, with increased number of GCP workshops being conducted
- Increased participation/contribution in various international multicentre studies, including early phase studies
- Advancement of local investigators' competencies and areas of expertise (e.g. diabetes, cardiovascular, nephrology, etc)

Malaysia is deemed competitive in terms of cost as well but the trend in increasing cost demand is observed in recent years, and this needs to be managed carefully.

The number of global studies being conducted in Malaysia has grown gradually over the years. However, the rate of growth lags behind other countries in Asia. If drastic action is not taken, the gap will expand further and Malaysia's involvement in global clinical trials may be deemed insignificant.

To achieve our objective to ***grow the volume of clinical trials by five fold***, the key challenges and gaps must be acknowledged, and solutions drawn are effectively implemented to remove the obstacles and barriers preventing our growth.

Areas of Opportunities To Drive Clinical Research Growth

The Clinical Research Working Group and CRM have identified the key areas to drive Clinical Research growth in Malaysia.

The **FOUR CRITICAL FACTORS** which must be reviewed and taken into consideration when planning and implementing any initiatives, projects, etc in these areas of opportunities are:

- *Develop research related processes, requirements and policies from the stakeholders' perspectives; engage key stakeholders in process development and decision making*
- *Derive practical and efficient value added solutions which promote acceptance and compliance; target root cause of the identified issue*
- *Communicate and implement identified solutions and/or initiatives in a coordinated, structured and consistent manner*
- *Track action items, deliverables and milestones against plan; measure effectiveness of initiative on an ongoing basis and refine as necessary; hold responsible individuals accountable*

Innovative ideas can be a difference-maker and must be thoroughly explored and considered to provide global sponsors compelling reasons to invest and conduct clinical trials in Malaysia. E.g.

- *Enable priority/expedited regulatory review timelines for new chemical entities (NCEs) which have Malaysian sites' contribution in the global studies.*
- *Enable priority review in the hospital formulary listing for global trials experience/participation in the government healthcare sector*
- *Introduce incentives (e.g. tax breaks)*

Strategic medium to long term plans need to be put in place to drive clinical research growth. As a collative voice of the pharmaceutical industry, we elaborate and share our perspectives on the **key areas of opportunities and identified needs and actions, which are the critical success factors in driving** towards achieving our target of **at least 1000 trials by 2020**.

1. Sites Set Up and Research Infrastructure

There is **limited number of sites with research set up and infrastructure to conduct high quality global clinical trials.** Constantly depending on the few reliable sites will not be sufficient and sustainable. When these sites are overwhelmed, potential mistakes and resource constraint at site will become an issue.

Identified Gaps

- Basic requirements for **research facilities** are still lacking in a number of sites or potential sites, e.g. computer/internet access
- **Medical records retention**, which is generally deficient at most sites currently, must be enhanced to meet internationally accepted standards and Malaysia GCP requirements
- In hospitals which use **electronic patient records**, applicable regulations (e.g. Code of Federal Regulations [21 CFR Part 11]) must be complied with
- **Administrative set-up** to support the administrative aspects of clinical trials is inadequate (e.g. processing of payments, clinical trial agreement signatory)
- Lack of **coordination between collaborating departments** (e.g. finance/accounts, local lab, etc)

Identified Needs and Actions to be implemented

- **Significantly increase the number of quality sites and rapidly build and equip new sites**
  - To be able to encourage and accommodate the expected exponential growth in clinical trials
- Provide **stable and efficient research infrastructure**, including Information Technology (IT) support and advancement
- Identify **priority areas for research funding**; develop **centers of research excellence**
- Identify and adopt **expected international standard accreditations** (e.g. IATA certification)
- **Study payment processing channel/set up** (e.g. trust fund, research account, etc) must ensure the following:
  - Transparency
  - Support payout to relevant parties (e.g. Study coordinators, local lab, etc)
  - Investigators should be able to mobilize the research fund under their study account for their department
  - Overhead charges should be reasonable and cover basic research facilities; maintain reasonable and competitive cost structure
- Promote **synergistic coordination** across all collaborating departments

2. Human Capital and Research Culture

In MoH sites, research activities often compete with clinical services for time and resources. Participation in global studies which require much commitment in terms of time and resources is often a challenge. This results in lack of interest amongst MoH physicians to be actively engaged in research activities.

Identified Gaps

- **Lack of incentives and motivation**
  - Currently most investigators and individuals working in research are not compensated nor recognized for their effort and time spent on research
- **Research culture is not embedded nor encouraged** in most MoH hospitals due to resource constraint
- **Reluctance to change or to move out from comfort zone** will not advance the research capabilities and standards
- Good sites are saturated and potential sites may **not be set up/equipped with the required human resources** to support the conduct of global research
  - Even if pharmaceutical companies would like to increase studies allocation to Malaysia, we will not be able to meet the demand and expectation with the existing resources

Identified Needs and Actions to be implemented

- Provide recognition to institutions/individuals for research initiatives and achievements in global trials contribution
  - Develop incentives and support for research staff to ensure that involvement in clinical research is appropriately rewarded
  - Allow payment for work done while maintaining a competitive cost structure
- Build a 'research culture' mindset in MoH sites
  - Promote research activities and curriculum
  - Develop career path advancement/opportunities for individuals with genuine and strong research interests
  - Support interested investigators to build their sites, and their research competencies
- "Protected time" for research (i.e. dedicated research time) for MoH investigators to allow them to spend sufficient time on committed research activities and ensure the study quality

3. Training and Development

Effective delivery of a **structured training and development plan** in Clinical Research is essential in building a pool of capable and high caliber research talent. There is a strong need to ensure the target number of trained investigators and study coordinators are available within the timelines set, to support the expected increase in number of clinical trials in Malaysia.

Identified Gaps

- **Insufficient sites with *committed and trained* site personnel** (investigators, study coordinators, etc) to conduct **high quality global clinical studies**.

Identified Needs and Actions to be implemented

- Thoroughly think through on the development strategies and training curriculum to expand the talent pool in Malaysia.
  - Engage and obtain input from key stakeholders in the development of such strategies and curriculum
- Increase pool of investigators and study coordinators with high level of interest and commitment in conducting research (not just list of GCP certified physicians)
- Have the 'right people on the job', i.e.
  - Investigators and study coordinators, etc with strong research interest and willing to spend time on studies and GCP requirements training, etc with sponsor.

4. Quality of Work and Deliverables

Study quality and data integrity are the 2 most important areas which cannot be compromised in the conduct of clinical studies. Hence there is a strong and urgent need to expand and build more quality and capable sites to support our objective in growing the number of trials in the country.

Identified Gaps

- **Lack of overall capability and quality at sites causing inappropriate demand of manpower resources on the part of sponsor**
  - Poor practical application and understanding of GCP principals despite training/ re-training
  - Often CRAs are required to spend more than expected time to oversee and repeatedly guide site personnel to ensure quality conduct of studies allocated. Such demand limits the potential to allocate more studies to the country.
    - E.g. a CRA in Hong Kong can manage 8 – 10 Hong Kong sites effectively, but the demand for resources may only allow a CRA to effectively manage 4 – 6 sites in Malaysia
    - In addition to posing additional resource demand to sponsor companies, there could be potential concern to place high complexity studies in the country as well.
- **Committed patient recruitment target is not delivered consistently**
  - There are currently insufficient sites with reliable track record. Sites must drive and aim to meet 100% of the committed recruitment target
  - ***Lack of accountability*** on delivering the committed patient targets will affect country's performance in the Key Performance Indicators (KPIs)
- **Quality of documentation could be further improved**
  - Despite good progress being demonstrated over the years, there are still plenty of rooms to ensure good documentation practices. E.g.
    - *Content of critical study documents such as IRB/IEC approval letters must be accurate*
    - *Study files and source documents (e.g. patient medical records) must be complete, accurate and maintained per GCP requirements*
- **Technical issues with research systems and databases** which are not resolved timely may result in potential GCP non compliance

Identified Needs and Actions to be implemented

- Sites should be **resourced and trained** to ensure continuous quality conduct of studies allocated, with **minimal need for 'hand holding'/supervision** from sponsors
  - Aim to develop self sufficient and quality site personnel.
  - Change in mindset required to improve efficiency and quality
- Hold individuals **accountable for delivery of expected responsibilities, quality** and **KPIs** (e.g. data quality, committed process change, patient recruitment target)
- **Good documentation practice** is a critical aspect of studies conduct. Countries and sites conducting global studies are expected to meet this requirement and generate quality data
- Technical issues need to be addressed in a timely manner to ensure **compliance to global standards** in research conduct
  - Incorporate quality mindset and build in quality systems and processes to minimize errors (e.g. IRB/IEC approval letters)
  - Encourage/reward for quality performance
- Perform **Users Acceptance Testing** (UAT) and ensure systems are:
  - Rolled out from the end users' perspective
  - User friendly and encourage compliance
- Implement new processes/systems only when they are functioning as they should, without compromising on any GCP or quality aspects

5. Research Network and Patients Pool Access

Lack of synergistic coordination between **Primary Care setting and Major Hospitals** to tap on the potential patient population is a gap which limits study patients recruitment.

Identified Gaps

- **Barriers across healthcare sectors** (e.g. referral network between primary care set up and major hospitals; private, government, universities) pose a challenge to improve study patients recruitment
- **Missed opportunities** to tap into the huge pool of patients in the primary care set up

Identified Needs and Actions to be implemented

- **Optimize the primary care network** and turn this into a competitive advantage for Malaysia
- Develop **seamless research network** to support growth in global research
  - Establish research networks and develop a coordinated approach in the conduct of clinical studies, allow rapid access to vast patient pool (e.g. patient database)
  - Partnership between Ministry of Health (MoH) – Public Health and Hospital Services, Ministry of Education, private and public sectors
  - Create opportunities for cross referrals whenever feasible (e.g. central recruitment/ reference centre)
- Leverage and build on the existing **Clinical Research Centers (CRCs) network**
- Prioritize development in the **Therapeutic Areas (TAs) of interest and high research potential**; concurrently, explore expansion/wider reach in other TAs and invest/expand accordingly
- Build **high integrity electronic patient database** that can be accessed throughout the clinical trial network

6. Timelines and Processes

CONSISTENCY in delivering the committed study KPIs is a critical factor which pharmaceutical sponsors consider in placement of studies, specifically on **study start up cycle time** and **patient recruitment target**. Countries' KPIs will be set and performance will be measured against target. Hence it's critical to ensure country's commitment is met.

Malaysia has been able to initiate studies within a very competitive (and predictable) timeline in the past. However, over the last 2 – 3 years, it has been consistently noted that the IEC/IRB approval timelines have increased and predictability has reduced. There is an urgent need to ensure we resume and even improve on our competitive edge in this critical area.

Identified Gaps

- **Inconsistent/unpredictable IRB/IEC approval timelines**
  - Most IRB/IEC's review/approval timelines were not consistent (i.e. approvals were not always received within expected/committed timelines), which makes study initiation planning difficult
  - An IRB/IEC approval/rejection letter could take up to 4 weeks to be issued after an IEC/IRB meeting
- **Lack of clarity and consistency in the approval process requirements results in unnecessary prolongation of approval timelines**
  - Some IRB/IECs' queries and requests are inconsistent and unpredictable, resulting in longer than expected submission/approval timeline
  - The unnecessary prolongation of study start up timeline will reduce the duration available for sites to recruit patients, which in turn will impact our competitiveness
- **Insufficient standard guidance on critical research processes**
  - E.g. study payment and contract management process
- **"Unsynchronized" roll out of initiatives/new processes, lack of performance tracking against plan**
  - Lack of clarity in implementation of processes related to clinical trial conduct and responsibilities
  - Insufficient tracking/measurement against objective, to review if an initiative/new process implemented is successful, or further refinement is required

Identified Needs and Actions to be implemented

- **Clear and consistent processes and requirements** must be in place to improve consistency and predictability (e.g. IRB/IEC SOPs)
- Maintain good discipline towards ensuring **accurate approval/rejection letters** are **issued promptly** (within committed timelines); **measure and track performance vs target**
- Despite good advances we have made in the IRB/IEC and Regulatory review/approval processes over the years, to increase our competitiveness, current **strengths must be further enhanced**, and **gaps must be addressed promptly**.
- **Increase IRB/IEC administrative support resources;** Provide appropriate training to the responsible person, utilize simple templates, have clear processes with target timelines in place

- Standardize, simplify and eliminate unnecessary steps/requirements for added advantage
  - Identify and remove unnecessary processes/red tape/policies to break the barriers
  - Shorten unnecessary review processes, remove documentation of limited value
  - Streamline and simplify processes in ***contracts and budgets finalization*** to allow prompt study start up
- Ensure effective implementation of new processes/identified solutions to an issue:
  - Crucial to have a good understanding on the issues hindering us to have the right solutions at hand; engage key stakeholders, stay focused on timely implementation of plans
  - Sufficient time shall be provided in preparation towards adopting/implementing any new policies affecting the conduct of research
  - ***Synchronized approach/effort*** towards ensuring clarity in the processes and requirements to all stakeholders is essential

7. Engagement and Communication

Communication is a key area which requires strong focus, to ensure the relevant stakeholders are engaged and informed as necessary.

Although the sponsors have contributed to the development of our clinical environment today, most companies have had a minor role in providing input or feedback to the carving of the trial environment of the future. Engaging the right stakeholders can open access to the most current information and ensure a wholesome approach. This is crucial towards making timely decisions and developing the right policies.

A **longer term view** in the EPP2 strategy would require us to be **well informed, fast evolving** to the changes of the global clinical trial front and having the **right solutions and/or policies in place** to secure a position as a **'preferred trial location'** ahead of the region.

Identified Gaps

- **Lack/ineffective communication channels**
  - Often lack of official/written communication to sponsors on clinical research processes/ policies changes
  - Incomplete distribution list; sponsor companies may be missed in critical communications (e.g. process/policy changes)
  - Channel/platform for communications may not be the most effective/appropriate option
  - If the right stakeholders are not receiving the necessary information in a timely manner (e.g. IRB/ IEC requirements/process change), this will impact studies' timelines resulting in unnecessary study start up delay
- **Lack of stakeholders engagement in process development and decision making**
  - Processes/policies carved may not be conducive to the expansion and growth of research activities in the country
  - Stakeholders do not see the services/"value add" obtained from some of the processes/fees imposed

Identified Needs and Actions to be implemented

- Improve **communication delivery channels**:
  - Establish an effective communication network and platform, including forums for discussions with all stakeholders involve in developing new processes/policies
  - Develop stronger collaborative links with industry, ensure ***commitment to productive collaboration*** – Dedicated industry liaison team:
    - Enhance collaboration between MoH and industry: create a more research focused and research friendly environment
    - Open and productive dialogues to ensure commitment from all parties to work towards the same objective
- **Officially communicate** (in writing) on the changes in clinical research requirements, processes or policies to all stakeholders
- Provide **clarity in the roles and responsibilities** and **rationale for changes** (e.g. how the new process will help to shape the research environment positively)
- Have the **right policies in place**
  - Evaluate the risk benefits of the policies and regulations that hinder the entrance of trial opportunities; modify or improve accordingly
  - This will make a positive impact in supporting and developing the clinical research environment
- Keep abreast of **global clinical research environment, evolution and trends**; draw an **effective local strategy** to support and ensure Malaysia's continuous participation and competitiveness in the changing environment
  - Ensure only processes that **add value** to improve our current systems are imposed/ implemented

Clinical Research Malaysia (CRM)'s Roles – Pharmaceutical Sponsors' Perspectives

CRM would serve best as an ***enabler*** and ***facilitator*** to clinical research activities in Malaysia. The following are the key roles which pharmaceutical sponsors envisioned CRM to play:

- *Facilitate and enable conduct of global research; promote and ensure compliance to local and global research standards*
- *Promote research culture; build Clinical Research talent pool and quality sites as described in the content of this whitepaper*
- *Proactive role in representing stakeholders' interest in formulation and implementation of policies affecting conduct of clinical research*
- *"Synchronize" implementation of identified initiatives; ensure timely communication and involve the appropriate stakeholders in process development and decisions making*
- *Track and measure implementation of identified initiatives against plan; refine as necessary*

Conclusion

The clinical research industry in Malaysia has vast potential to grow. Not only does this bring **foreign revenue and jobs** into the country, it enables investigators and patients early access to the latest and novel treatments available. We have the necessary workforce and population to sustain a very healthy clinical research environment. The major challenges lie in **boosting the capabilities of our sites and people** to the next level, and removing the 'red tape' which may hinder our growth.

The pharmaceutical industry has a common goal as the Performance Management & Delivery Unit (PEMANDU), i.e. to **position Malaysia as 1 of the key countries in the 'research map' for global trials allocation.** We need to continuously **outperform, meet or exceed our targets**, while maintaining **quality output**, hence making Malaysia an attractive location regionally/globally to conduct world class clinical research.

CRM can partner with the key industry stakeholders to further develop the research sites within Malaysia. We need to synchronize and consolidate our effort and resources, to facilitate and enable conduct of quality global research.

Continuous discussion and productive collaboration is vital to keep all stakeholders' objectives aligned. CRM can echo the voice of the industry in implementing changes to the current practices and policies that are still plagued with inefficiencies, bureaucracy and poor allocation of resources. Although activities to promote Malaysia as a clinical research destination are laudable, more effort at the ground level is needed to ensure Malaysia delivers the results.

Gaps that can be addressed immediately, or areas of enhancements that are readily achievable without needing major investment should be reviewed and acted upon promptly.

Quality, Consistency coupled with ***Competitive timelines and cost structure*** will be our key to success in achieving the target to grow the clinical research industry.

This paper summarizes the key stakeholder, i.e. the pharmaceutical sponsors' perspectives, on the **identified needs and required actions** to fast track the clinical research industry in the country. Acknowledgment of the stakeholders' needs and desire to change will ultimately lead us to meet our objectives in terms of job creation and revenue generation.