Clinical Research Footprint and Strategic Plan to Promote Clinical Trials in Belgium

Giving impetus to clinical trials in Belgium

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for:
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At a glance – our views

Against the backdrop of global trends, challenges and a changing clinical trial model, Belgium currently still holds a competitive position within Europe. We perform well on approval time, quality and expertise; all key drivers for clinical trial location choice.

Despite this, the number of clinical trials in Belgium is in decline. Eastern Europe and emerging countries outperform Belgium’s clinical trial cost and access to (and recruitment of) patients, which remain a challenge in Belgium.

Clinical trials are a cornerstone of the Belgian (knowledge) economy and provide patients with early access to innovative medicines. It is therefore imperative to maintain and further strengthen Belgium’s clinical trial position. While several initiatives have been made to attract more trials locally, a clear strategic objective and central coordination is lacking.

Although the future environment will undoubtedly pose real challenges on clinical trials, there are also clear opportunities to boost clinical trials in Belgium.

Based on a thorough benchmark with other countries, building on the identified opportunities presented by the future environment and drawing from recommendations gathered in a stakeholder survey, we present a strategic plan built on three key initiatives. It aims at promoting clinical trials in Belgium and concludes with the formulation of clear, actionable recommendations to all stakeholders involved (Figure 1).

Figure 1: Strategic plan to promote clinical trials in Belgium.

3 key strategic initiatives to promote clinical trials in Belgium

1. Standardisation (‘one-stop-shop’)

2. Network of specialised centres

3. Supportive governmental framework

This report can be downloaded in full at www.pwc.be/pharma.
To measure is to know: 2012 study to assess the footprint of clinical research and the attractiveness of Belgium

There is more to clinical research than meets the eye. While clinical research first and foremost helps turn new drug candidates into medicines that can significantly improve or save our health, it also helps create extra employment and economic benefits in the host country. In Belgium alone, the pharmaceutical sector accounts for some 32,200 jobs with around 4,600 in R&D.

A key component of clinical research is the conduct of clinical trials. For patients, participating in clinical trials can offer early access to medicines that have already been tested for safety but are not yet available to them on the market.

Belgium historically holds a strong leadership position in clinical trials. Today, it is still the number-one European country in terms of per capita participation in trials, holding a share of no less than 9%. This is largely due to an impressive qualitative network of researchers, academic and non-academic research centres and a range of pharmaceutical companies established in Belgium.

The last decade, however, China, India, South America and the Central and Eastern European countries have fast been entering the clinical trial field, benefiting from the presence of large patient populations and a comparatively low cost basis. The number of trials in the Central and Eastern European region, for instance, grew 3-fold between 2002 and 2007. In India, the cost of a clinical trial is half of that in the US.

In order to secure and preferably even strengthen Belgium’s position in this arena, ‘The Initiative to promote clinical trials in Belgium’ (“the Initiative”) was launched early 2010. The founding associations were the Belgian Association of Clinical Research Professionals (ACRP.be), the Belgian Association of Pharmaceutical Physicians (BeAPP), the Belgian Association of Phase 1 Units (BAPU) and pharma.be. These associations joined forces with the strategic intention to build a sustainable and high-performing clinical trial environment in Belgium.

The Initiative first commissioned PwC in 2011 to map the global and Belgian clinical trial situation. As a continuation of this project, the Initiative recently commissioned PwC for a more thorough assessment. The aim was first to determine the economic, societal and competitive footprint of clinical trials in Belgium, to understand the drivers for clinical trial location choice, to assess the attractiveness of Belgium as a location for clinical trials and finally, to formulate an actionable strategic plan for the promotion of clinical trials in Belgium.

The key findings in this report are based on the analysis of 3 information sources:

- selected 2011 data of the Clinical Trials Application (CTA) database from the Belgian Federal Agency for Medicines and Health Products (FAGG-AFMPS);
- an online survey, conducted in January-February 2012, with 53 stakeholders involved in clinical studies, including pharmaceutical industry representatives, academia, patient organisations, clinical in- and outsourcing providers, ethics committees, hospital directors, clinical investigators and government authorities;
• a comparative benchmark exercise with other EU countries on initiatives towards attracting more clinical trials.

This report, whose highlights were presented at the Belgian Pharmaceutical Conference on 17 April 2012, summarises the findings and outlines the strategic plan towards promoting clinical trials in Belgium.

The first chapter of our report highlights how global market forces impact clinical research on a global and European level. It also covers the recent trends in clinical in- and outsourcing and outlines the initiatives taken by several European countries to attract more clinical research.

The second chapter sets out to describe the status and evolution of clinical research in Belgium, the significance of clinical trials to the Belgian (knowledge) economy and the current local initiatives to attract more clinical trials.

The third chapter investigates how decisions on where clinical trials will be conducted are made and by whom. It looks at drivers for location choice and assesses the key drivers and deterrents for choosing Belgium. The chapter concludes with an overview of Belgium’s attractiveness as a clinical trial location compared to other European countries.

The final two chapters conclude with the key stakeholder recommendations and an actionable strategic plan to promote clinical trials in Belgium. The plan covers key opportunities to boost clinical trial activities based on trends and evolutions towards the new environment. Three strategic initiatives and stakeholder actions will form the basis for attracting more clinical trials.
The global clinical development research model is changing

Europe is still a research stronghold

Investment in R&D is known to have a positive impact on the health and wealth of a nation and to long-term economic growth\(^2\). Europe today is fortunately still a research stronghold. In 2010 the research-based pharmaceutical industry invested approximately €27 billion in R&D in Europe, making the pharmaceutical industry the largest R&D sector within Europe\(^9\). It directly employs 640,000 people and generates three to four times more employment indirectly.

Since 2005, the levels of pharmaceutical R&D spending in Europe are comparable to those in the US, which has historically been much stronger. Over the period 1995-2005, the US pharmaceutical market grew almost twice as fast as the European market with a significant shift of pharmaceutical R&D activity towards the US This decade of strong US market dominance has since come to a halt (Figure 2)\(^1,10\).

**Figure 2**: Annual Growth Rate of Pharmaceutical R&D Expenditure in Europe and the US

Growing pressure on R&D spend

Blockbuster patent expiry exposes many of the leading pharmaceutical companies to significant revenue declines\(^3\). This leads many to resort to cost-cutting initiatives and reductions in R&D expenditure. More recently, the economic downturn also had its impact. For the first time in 40 years, global pharma R&D spending declined in 2009 (Figure 3)\(^3\).
Today, the sector faces further challenges: beside increasing regulatory hurdles and escalating R&D costs, the sector has been severely hit by austerity measures introduced by governments across much of Europe in 2010 and 2011. On top of this, prices of medicines in the EU are not governed by free competition laws, but fixed by the government on a national level. This has resulted in a lucrative parallel trade between countries with significant price differences, estimated to amount to €5,200 million (value at ex-factory prices) in 2009 alone. This benefits neither social security nor patients and deprives the industry of additional resources to fund R&D\textsuperscript{10}.

### Rising clinical trial costs consume majority of R&D budget

In 2009, European pharmaceutical companies reinvested an average of 18\% of their sales into R&D. The majority of this budget was spent on clinical trials and roughly a quarter on pre-clinical research\textsuperscript{1, 10}.

The percentage share of total R&D budget allocated to clinical trials has increased considerably over the last few years,\textsuperscript{1, 10, 11, 12} (Figure 4). This is not surprising, given that the complexity of clinical trials, measured by the mean number of procedures per patient, is on the rise across all phases of clinical development\textsuperscript{13}.

There is also a growing focus on niche treatments, causing more difficulties in recruiting and retaining patients that meet specific criteria\textsuperscript{14}. At the same time, many new drugs present only incremental improvements, meaning larger numbers of patients are needed to adequately demonstrate those smaller additional benefits. Other drivers of clinical trial costs include a greater emphasis on data and site monitoring, increased use of technologies (e.g. diagnostic tools, genetic profiling tests etc.) and the delays caused by the many parties involved in the regulatory authorities and ethics committees\textsuperscript{15}. 

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**Figure 3**: Pharma R&D spend over time

<table>
<thead>
<tr>
<th>Year</th>
<th>R&amp;D Spend as % of Revenue</th>
</tr>
</thead>
<tbody>
<tr>
<td>1970</td>
<td>0%</td>
</tr>
<tr>
<td>1980</td>
<td>10%</td>
</tr>
<tr>
<td>1990</td>
<td>20%</td>
</tr>
<tr>
<td>2000</td>
<td>30%</td>
</tr>
<tr>
<td>2010</td>
<td>40%</td>
</tr>
</tbody>
</table>

As a result of the economic downturn, global R&D spend declined in 2009 for the first time in 40 years.
Rising costs and increasing budget pressures have started to affect clinical trials, forcing companies to rethink how to perform these activities in the (near) future.

**Emerging ‘live licensing’-based clinical trials**

To address budget pressures, pharmaceutical companies are looking for new and creative ways to generate revenue streams faster. A flexible framework based on ‘live licensing’ as described in our ‘Pharma 2020: Virtual R&D’ report will be an answer. It proposes a step-wise approval during the development of the product, replacing the cumbersome, all-or-nothing approach at the end of development. Once there is sufficient evidence that a medicine works and is cost-effective in the initial trial population, the regulator can already allow the company to market the treatment on a restricted basis. At a later stage the population can be further enlarged when additional evidence and approval are given. This ‘live licensing’ framework will enable a company to reduce its time to market and earn revenue sooner.

‘Live licensing’ will impact the type of clinical trials and the way in which they are conducted. There will be more small-scale trials and trial designs will have to be more flexible. Due to an increased demand for post-approval and continuous data-gathering, we will also see an increase in the number of Phase IV trials to collect clinical performance evidence throughout the whole product lifecycle.
Development of stratified medicines affects clinical trial design and capabilities

In a bid to find new ways to lower healthcare cost, many countries are exploring the potential of Pay for Performance (P4P) systems in which reimbursement will be directly linked to therapeutic outcomes\(^6\)\(^-\)\(^7\). Pharmaceutical companies therefore increasingly focus on ways to identify patients that are more likely to benefit or experience an adverse reaction in response to a specific therapy. This would enable them to better match patients with therapies and thus improve therapeutic outcomes. Matching therapies with specific patient populations through the use of, for instance, biomarkers, also called stratified medicine, is anticipated to have a major effect on both clinical practice and the development of new drugs and diagnostics\(^3\)^\(^2\). Translational research is a key capability for the development of stratified medicines\(^8\). It makes use of combined data from various disparate sources and translates them into new discoveries. Examples of such sources include correlation studies, biobanking data, (in-vitro) diagnostic tools, combinational pattern analysis, electronic medical records, health information technology etc. Translational research has already taken off globally with major activities in the US and Europe, both in early R&D and clinical research. It fosters the collaboration between hospitals, pharmaceutical companies and payers, which creates new dynamics and insights and gives rise to networks of expertise centres.

The development of stratified medicines also affects clinical trial design. It requires specific clinical trial designs for patient groups with a defined genetic profile. As a consequence, more complex, smaller-scale clinical trials will have to be set up.

Empowered patients demand transparency and more say in the clinical trial process

The development of stratified medicines will enable us to gain further knowledge and insight in diseases. This knowledge will not merely reside with a select group of scientists, but will also expand towards patients. As we are living in a fast-changing world where information-sharing grows exponentially, patients will become better informed on diseases and their health state. Patients are already grouping themselves in networked communities supported by social media to express their expectations and concerns. Patients want to receive clear information on the purpose of the trials and how it will affect them but will also demand transparent data-sharing and involvement in decision-making. These pressures will modify the way clinical trials are performed.

A shift towards in- and outsourcing

As the management of clinical trials becomes progressively costly and complex, many pharmaceutical companies resort to outsourcing their clinical trials to clinical research organisations (“CROs”). This trend is also reflected in our current survey, with a large majority relying on outsourcing (94%) and insourcing (63%) services for clinical studies.

Outsourcing is the process of contracting an independent organisation to perform tasks (e.g. clinical trials) and ceasing to perform that activity internally. Insourcing is the opposite. Rather than buying services, you obtain the resources to provide the service internally. Outsourcing can help make a company less prone to the constant fluctuations in the modern R&D cycle, by enabling better control of budgets and resources.

Pharma companies will become more accountable to decrease the rising healthcare costs. This will lead to the development of stratified medicine and new related ways to perform clinical trials.
In- and outsourcing decisions are traditionally driven by cost factors, but pharmaceutical companies also look to improve efficiencies, mainly in terms of flexibility and resource and portfolio management. The decision to outsource clinical trials depends also on the type of study. Exploratory studies (Phase I and II) often require specific expertise that is not always readily available in-house and are most commonly outsourced (Figure 5). Companies mostly outsource operational aspects like administrative tasks, trial monitoring, trial management, data management and contract management (Figure 6).

**Figure 5: Most outsourced type of clinical trial**

![Bar chart showing the most outsourced type of clinical trial](chart1.png)

*Source: PwC survey, 2012*

**Figure 6: Most outsourced clinical trial aspects**

![Bar chart showing the most outsourced clinical trial aspects](chart2.png)

*Source: PwC survey, 2012*
When asked about their outlook for the next five years (2012-2017), CROs expect to be confronted with significant changes, most notably a further increase in globalisation and competition. Pharmaceutical companies, on their part, foresee an increasing reliance on in- and outsourcing services and activities. Already today, this trend represents a fundamental shift away from the industry’s tradition of strong vertical integration. While the benefits of outsourcing in the shorter term are clear, the long-term impact of lifting key R&D expertise outside of the company structure and exposing knowledge generated through the outsourced projects to other parties will need to be considered carefully. Moreover, with ‘live licensing’ and the demand for extended data collection throughout the product life cycle, a different collaboration model between pharma companies and in- and outsourcing providers will have to be developed.

Although a majority of in- and outsourcing providers and pharmaceutical companies indicate working on a preferred provider basis, strong strategic alliances are far and few in between. The stakes are high for both parties involved. Providers capable of forging long-term vested alliances with their clients will be better positioned to weather the likely increasing competition and pressures on cost structures.

**A shift towards emerging countries**

As clinical trials become increasingly complex, the cost of conducting clinical trials will continue to rise. Pharmaceutical companies therefore increasingly look to emerging countries, most notably the BRIC countries (Brazil, Russia, India and China), for solace.

In 2010, the Brazilian pharmaceutical market grew 20.1% and the Chinese market even 21.9%. Comparing this with an average market growth of 1.8% for the five major European markets and 3.3% for the US, it is clear that the geographical balance is shifting to the East. It is anticipated that the pharmaceutical markets in the emerging countries will continue to grow another 14-17% by 2014, compared with 3-6% for major developed markets.

Pharmaceutical market growth is a key reason for the shift of key clinical trial activities towards emerging countries, but it is not the only one. The emerging countries are progressively attracting clinical trials due to low costs, the availability of a skilled R&D workforce, the objective of market entry and large patient populations. These patient populations are often treatment-naive, easily accessible and can quickly be enrolled.

In China and India the cost of conducting clinical trials is 50% cheaper for Phase I and 60% cheaper for Phase II/III compared to the West. In China, the Government is concentrating on drug development as a strategic industry. Grants and loans are readily available under multiple programmes. China also has a cheap and skilled R&D workforce. The National Bureau of Statistics of China indicates that the number of university students in China has increased rapidly in recent years, from 17 million in 2003 to 119 million in 2010. As the country continues to scale up its recruitment for higher education, this figure will keep growing.

India, meanwhile, has instated regulations that provide fiscal incentives for R&D activities. The Indian pharmaceuticals market will be one of the top-10 sales markets by 2020. India’s population is growing rapidly, as is its economy – creating a large middle-class able to afford a broader range of medicines. Its total market is expected to rise to a value of approximately US$50 billion by 2020, which will undoubtedly attract R&D activity within the country.
Taiwan also introduced different regulations and policies to stimulate the pharma and life sciences industry. The Taiwan Food and Drug Administration, for instance, simplified application procedures and loosened regulations for drug registration and market approval in order to accelerate the process to sell new drugs in the market and promote the export of domestically manufactured drugs\(^{18}\). Moreover, the government of Taiwan is allocating billions on biomedical research and the creation of science parks\(^{16}\).

All these factors combined have created a highly favourable clinical trial climate in emerging countries, rivalling the West. This is reflected in our survey, with pharmaceutical companies reporting a shift of confirmatory clinical trials from the US, Western and Eastern Europe to the BRIC countries these last 5 years (2006-2011). Companies anticipate a decline in number of clinical trials by about 20% over the next 5 years (2012-2017) and a further shift of confirmatory trials towards the BRIC countries. Exploratory clinical trials (Phase I and II), however, are anticipated to remain in the US and the EU.

**Initiatives taken by European countries to attract more clinical trials locally**

To maintain and strengthen their position in the global clinical trials market, several European countries have already started concerted efforts to strengthen their pharmaceutical R&D position and attract more clinical trials locally. While some countries focus on improving the local legal framework for clinical trials, others invest in clear guidelines and more transparent communications or on improving access to patients and networks of clinical trial centres. In many countries, the initiatives are initiated by both the pharmaceutical industry and the local government.
More recently, Nefarma, the association for innovative medicines in the Netherlands, has taken several initiatives to improve the local clinical trial climate. The initiatives are focused on improving Dutch law and regulations on clinical trials and on ameliorating the infrastructure of Dutch clinical trial centres. The key aim hereof is to shorten clinical trial approval times and accelerate access to medicines. To date, these efforts have resulted in standardisation of patient information forms, clinical trial agreements, financial negotiation formats, a single standardised insurance for patients participating in clinical trials nationwide, the development of best practice guidelines and a new guideline on multicenter trials (effective as of 1 March 2012). Local hospitals are encouraged to set up a dedicated Clinical Trial Office, and to certify and professionalise their investigators.

As early as 2007, the public interest group CeNGEPS was founded in an effort to bring together the main public and private clinical research stakeholders in France. The objective of CeNGEPS is “to recruit much, much faster and better” for clinical trials by supporting investigators and a national network of 18 specialist research centres. Key actions include promoting clinical research to public authorities, professionals and patients; harmonising procedures to shorten the set-up time of clinical trials; providing human resources to support investigators (e.g. nurse network); supporting a national clinical research network and allocating Clinical Trial Points of Contact in interregional clinical research and medical centres. The initiative is funded through national subsidies that were raised as tax on the revenue of pharmaceutical companies. This means that clinical trials sponsored by academia and trials conducted by smaller start-up companies also benefit.

In 2010, the pharmaceutical industry in Poland (represented by INFARMA) together with the Association for Good Clinical Practice (GCPPI) embarked on a series of advocacy activities towards selected decision-makers, politicians, experts and key opinion leaders. The aim is to raise awareness on the local clinical trial situation and possible scenarios for growth, as described in our “Clinical Trials in Poland – Key Challenges’ report”. This culminated in the development of an industry self-regulation on clinical trial conduct and the scheduled launch of a public website of newly registered trials in Poland.

On a European level, clear positive measures were made towards patients (and indirectly also to the pharmaceutical industry) with the creation of the EU Clinical Trials Register. Since March 2011, EU citizens have direct access to information on clinical trials conducted in Europe. The website www.clinicaltrialregister.eu provides public access to information extracted from the EU clinical trial database EudraCT and enables patients to be informed and enrolled in clinical trials. It is expected that this information-sharing will encourage more patients to become more involved in clinical trials in an attempt to have early access to new therapies. As such, this is expected to have a favourable impact on the attractiveness of Europe for clinical trials.
In terms of performance, Belgium must remain vigilant

Belgium holds a competitive position in number of trials and trial density

Belgium historically holds a strong competitive position in the global clinical trial scene. Based on the number of clinical trials submitted as the basis for marketing authorisation applications to the EMA between 2005-2009\(^9\), Belgium belongs to the top-10 clinical trial countries, ranking ninth (Figure 7).

\textit{Figure 7}\(^9\): The number of pivotal clinical trials in MAA submitted to the EMA in the 2005-2009 period, for the top-20 countries.

On a global scale, Belgium belongs to the top-10 countries with the highest amount of trials submitted in marketing authorisation applications.

Belgium comes in on the 13th place (Figure 8) based on number of clinical trial sites per country worldwide\(^9\). When comparing only the European countries, Belgium ranked seventh.
Moreover, Belgium is one of the world’s leading countries in terms of clinical trial site density, measured by number of sites per 1 million population. Belgium holds a praiseworthy second place, leaving only the US ahead (Figure 9). Comparing Belgium with its neighbouring countries shows that the Netherlands are not so far behind with an eight-percent lower density, while Germany and France are lagging almost 50% behind.

**Figure 9**: Clinical trial site density per country in 2008, for the top-20 countries.
Eastern Europe and emerging countries outperform Belgium in clinical trial cost

Based on a PwC analysis performed in 2010, Belgium also scores well compared to other European countries and the US with respect to the cost of conducting clinical trials (Figure 10). This notwithstanding, Eastern Europe and Asia operate at a considerably lower cost: the cost of conducting clinical trials in Belgium is 18% higher compared to Hungary and India and more than 20% higher compared to China and Russia.

Figure 10: Average cost of clinical trials per country in 2010, with the US as benchmark

Cost differences between the CEE and Western Europe used to be larger than today, both in terms of fees and operational expenses. Despite this converging trend, which is in line with overall economic development, the costs in Eastern Europe and emerging countries still outperform Belgium’s clinical trial cost.

Patient recruitment in Belgium remains a challenge

Patient recruitment and retention in clinical trials are widely recognised as the leading bottleneck in the clinical development process. Patients or volunteers are the backbone of every clinical study. Until recently clinical studies are becoming larger, longer and more complex. This evolution required more patient participation than ever before, as sufficient patient retention from the time of study initiation to closeout is needed to derive conclusive proof.

When comparing the number of patients participating in clinical trials, Belgium ranks lower compared to the other countries. This can be explained by the relatively limited patient population available in Belgium, compared to other countries. When these figures are expressed per capita, however, Belgium emerges as one of the countries with the highest participation rate in Europe.

Patient organisations can play a key part in the recruitment process by raising awareness and assisting in the provision of tools for recruitment (registries, portals, etc.).
Despite a competitive position, the number of clinical trials in Belgium is in decline

Despite Belgium’s historic stronghold in the global clinical trial market, the total number of clinical trials has reached its lowest level since 2006 (Figure 11). After a peak in 2008, a continuous decline of approximately 20% in the last 4 years was observed, with a loss of 4% this last year alone. The decline is largely due to a loss of industry-driven trials (i.e. trials initiated and sponsored by the pharmaceutical industry) over the past 5 years.

**Figure 11**: Total number of clinical trials per year in Belgium

Looking at the breakdown of these numbers in individual trial phases (Figure 12), we note that the number of exploratory trials (Phase I and II) has remained relatively stable. These trials investigate the more fundamental aspects of the medicine at an early stage, such as pharmacokinetics and pharmacodynamics, the safety and first evaluation of dose and effect. These studies can be performed in a small number of patients but require a specialised organisational set-up and specific expertise.

The majority of clinical trials in Belgium are Phase III trials. These are conducted on much larger patient populations to assess whether the medicine has the desired therapeutic effect. While these trials provide large numbers of patients with early access to innovative medicines and can as such contribute to the welfare of patients, the number of Phase III trials in Belgium has decreased by 6% over the last year.

The number of Phase IV trials, on the other hand, has increased by 8% since 2010, most likely due to post-approval commitments and follow-up studies.
It is important to note that input gathered from pharmaceutical companies and CROs in our survey, reflects the increase in outsourcing activities with industry reporting a decline of number of trials conducted in Belgium by around 10% over the last 5 years (2006-2011) while CROs have observed an increase of trials locally by about 25%.

**Majority of clinical trials in Belgium is industry-driven**

Mirroring the trend in other European countries, a large majority of clinical trials in Belgium is industry-driven (Figure 13). These trials also generate the most significant investment and employment opportunities for a country.
Belgian hospitals responding to our survey report to have recruited 8 times more patients for exploratory industry-driven trials conducted in their hospitals than for exploratory investigator-driven trials. For confirmatory trials, the difference is even higher, by 20-fold.

Industry-driven trials in Belgian hospitals were mostly Phase III, II and I, while investigator-driven trials were mainly non-interventional studies and Phase IV (Figure 14).

**Figure 14: Ranking of clinical trial types in Belgian hospitals**

![Diagram showing the ranking of clinical trial types in Belgian hospitals.](image)

Source: PwC Survey 2012

**Number of amendments is increasing**

Pressures on R&D spend are pushing pharmaceutical companies to try and obtain results of clinical trials faster. Consequently, there is a growing tendency to submit protocols that are not yet fully mature, necessitating more amendments throughout the approval process.

When looking at the number of trial amendments in Belgium over the last five years, we observed a strong increase (Figure 15), reflecting increasing time pressure on the clinical trial process with early submission for approval and subsequent adaptations of the protocols.
Approval timelines are a key advantage of Belgium

Before a clinical trial can start or when an amendment is made, approval needs to be obtained from the competent authority and the ethics committee. The better and faster this process is organised, the sooner a company or an academic institution can commence its clinical research activities. The flowchart below gives a schematic overview of the approval process in Belgium.

The request for approval can be submitted to the competent authority and the ethics committee in parallel. The trial cannot start until both instances have given a positive advice28.

In Belgium, the legal approval timelines1 for the competent authorities and ethics committees are 15 days for Phase I trials and 28 days for Phase II, III and IV trials. Recent data indicates that this approval time is well respected for all phases (Figure 1720) with 12 and 22 days respectively.

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1 The FAGG approval time corresponds to complete file submission until the final approval of the dossier. The time for providing additional information in order to complete the dossier and the time to respond to objections (‘clock-stop period’), has been excluded from this calculation.
Figure 16: Schematic overview of the approval process for clinical trials

Figure 17: Average number of days from request to approval

These short approval times are a key advantage of Belgium compared to other European countries: the EC Directive on clinical trials, published in 2001, states 60 days as maximum approval time.
No shift in distribution of clinical trials across therapeutic areas

In Belgium, the number of clinical trials in ‘Antineoplastic and immunomodulating’ is the largest; within this domain approximately 80% is dedicated to cancer research. At roughly the same level, we find the Phase I clinical trials over all therapeutic domains. Due to their specificity they are reported separately. There was no noticeable shift in this distribution in recent years (Figure 18)\textsuperscript{20, 31}.

\textit{Figure 18\textsuperscript{20, 31}: Clinical trials per therapeutic domain in Belgium, Phase I research is reported separately due to the specificity and importance of this type of research}

<table>
<thead>
<tr>
<th>Therapeutic Domain</th>
<th>2006</th>
<th>2008</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antineoplastic and immunomodulating (incl. cancer research)</td>
<td>20.2%</td>
<td>20.1%</td>
<td>22.5%</td>
</tr>
<tr>
<td>Phase I (all therapeutic domains)</td>
<td>27.8%</td>
<td>22.8%</td>
<td>20.9%</td>
</tr>
<tr>
<td>Alimentary tract and metabolism</td>
<td>8.0%</td>
<td>7.8%</td>
<td>9.7%</td>
</tr>
<tr>
<td>Nervous system</td>
<td>8.6%</td>
<td>8.4%</td>
<td>8.3%</td>
</tr>
<tr>
<td>Cardiovascular system</td>
<td>7.8%</td>
<td>5.9%</td>
<td>5.3%</td>
</tr>
<tr>
<td>Musculoskeletal system</td>
<td>4.7%</td>
<td>3.6%</td>
<td>4.8%</td>
</tr>
<tr>
<td>Respiratory</td>
<td>4.5%</td>
<td>5.6%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Blood and blood forming organs</td>
<td>3.3%</td>
<td>5.3%</td>
<td>6.4%</td>
</tr>
<tr>
<td>Genito-urinary system and sex hormones</td>
<td>3.7%</td>
<td>2.3%</td>
<td>3.1%</td>
</tr>
<tr>
<td>Various</td>
<td>2.3%</td>
<td>3.3%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Anti-infective for systemic use</td>
<td>0.4%</td>
<td>4.1%</td>
<td>5.1%</td>
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<td>Sensory organs</td>
<td>0.6%</td>
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<td>1.3%</td>
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<tr>
<td>Dermatologicals</td>
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<td>Vaccine</td>
<td>1.8%</td>
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<td>6.5%</td>
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<tr>
<td>Other</td>
<td>4.4%</td>
<td>4.3%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

Clinical trials are a cornerstone of the Belgian (knowledge) economy

Clinical trials are an important aspect of the clinical research and health innovation activities in almost every country. Clinical trials generate employment and contribute significantly to the local economy. They also produce new knowledge and help translate that knowledge into better ways to treat diseases and improve healthcare. Lastly, clinical trials provide patients with early access to innovative medicines.

Clinical trials provide economic benefits to the host country

Although Belgium represents only 2.7% of the European GDP, its pharmaceutical industry represents a comparatively larger share of employment (4.9%) and R&D investments (6.6%) within Europe. In 2010 alone, pharmaceutical companies invested an estimated €1.8 billion in R&D in Belgium and now directly employ 32,200 people of which 4,600 in R&D\textsuperscript{29}. 
Clinical trials constitute a significant share of these investments and employment. Many stakeholders benefit from clinical trials as an additional source of income. Hospitals surveyed report that an average of 13% of the hospital budget is income from industry-driven clinical trials and that 74% of clinical trial FTEs in the hospital are allocated to industry-driven trials.

**Clinical trials contribute to local knowledge**

Clinical trials generate significant investments in education and professional development of researchers. Belgian pharmaceutical companies and CROs surveyed indicate that a further decline in clinical trials would impact their organisation in the form of job losses, leading to a loss of expertise and qualified staff in R&D. On the long term this may negatively affect innovation and reputation and it will be more difficult to attract and employ highly skilled workers. Clinical trial and research units would have to be closed down resulting in a further drain of the local expertise that has been built up in the field of clinical trials over the recent decades.

**Clinical trials provide early access to innovative medicines**

For patients, participating in clinical trials can mean early access to innovative treatments that are not yet widely available. In 2010, over 27,000 patients took part in clinical trials in Belgium, receiving free, early access to the latest treatments.

It is clear that an environment that facilitates and attracts investments for clinical trials contributes to the health and wealth of a nation and to long-term economic growth. As such, a further decline in the number of clinical trials is likely to have numerous tangible and intangible effects on the Belgian (knowledge) economy and its patients. It is therefore imperative that Belgium should undertake coordinated initiatives to maintain and strengthen its position within the clinical trials market.

**Belgian initiatives to attract more clinical trials lack a clear strategic objective and coordination**

**Federal initiatives focus mainly on general tax measures**

On the federal level, several tax measures were taken to stimulate the local research environment. Companies investing in R&D and employing highly educated researchers could benefit from tax exemptions on profits up to a certain proportion of the total investment value (including research costs).

Finally, to help companies attract talent, a federal law change was effectuated so that residence permits now suffice to employ researchers from abroad.

**Regional initiatives focus on investments and partnering**

On a regional level, the Flemish government allocated additional funding to innovation and development. Life sciences and health care is one of the 6 strong domains in which Flanders intends to invest (other pillars include logistics and nanotechnology). More recently, a Life Science Platform was launched to stimulate the research climate and the Centre for Medical Innovation (CMI) was founded to develop Flanders as a medical expertise region.

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2 Caveat: based on only few complete responses and mix between university and regional hospitals
As part of the Marshall Plan, the Walloon government has made funds available for the 5 competitiveness poles of the Marshall Plan, including BioWin as the ‘health’ pillar. It launched the Biowin initiative to stimulate concrete partnerships between the academic world and companies in priority therapeutic fields.

While these incentives focus on stimulating the overall research environment, few directly support the development of a more favourable clinical trial environment.

**Launch of the Initiative to focus on promoting clinical trials**

In order to secure and preferably even strengthen Belgium’s position in this arena, ‘The Initiative to promote clinical trials in Belgium’ (‘the Initiative”) was launched early 2010. The founding associations were the Belgian Association of Clinical Research Professionals (ACRP.be), the Belgian Association of Pharmaceutical Physicians (BeAPP), the Belgian Association of Phase 1 Units (BAPU) and pharma.be. These associations joined forces with the strategic intention to build a sustainable clinical trials environment in Belgium.

Since then, some progress has been made by pharma.be towards the standardisation of documents (e.g. informed consent, contracts, etc.) and professionalisation of the field (e.g. development of a dedicated website and a working group with key stakeholders).

**Clear formulation of objectives and coordination are required**

To date, initiatives occur mainly on an *ad hoc* basis. Most of the initiatives described above were taken several years ago and there has been little follow-up since. To enable Belgium to maintain and strengthen its position in the global clinical trials market, a clear strategic objective will need to be formulated so that effective differentiating actions can be identified and developed within a larger strategic framework. Equally as important is the instalment of a form of central coordination. On both these aspects, Belgium is lagging behind many other European countries like France and the Netherlands, in the race to attract more clinical trials in the future.
According to stakeholders, Belgium scores high on key drivers for clinical trial location choice but struggles with cost and access to patients

To develop a strategic plan to reverse the decline in clinical trials in Belgium and strengthen its position within the market, it is vital to understand the drivers for clinical trial location choice and gain insight in how attractive Belgium’s clinical trial features are perceived to be along these drivers. 53 clinical trial stakeholders and decision-makers were probed on their decision-making process and drivers for clinical trial location choice. Respondents were also asked to rate Belgium on a range of criteria relative to other European countries.

Decisions on clinical trial location are mostly taken by head office

Not surprisingly, the decision on which country the clinical trial should be conducted in lies most often with the head office of a pharmaceutical company rather than local affiliates. When pharmaceutical companies outsource their clinical trials (or parts thereof) to CROs, the decision is most often made jointly (56%). In only a minority of cases is the CRO the sole responsible for location choice (Figure 19).

Figure 19: Decision-making on clinical trial location

"Who typically decides on the clinical trial location?"

- 56% Pharmaceutical Company
- 32% Jointly
- 12% CRO

Source: PwC survey 2012
Time, cost and access to patients are key drivers for clinical trial location choice

On a general level, decisions on clinical trial location are driven by factors like time, cost, expertise, quality, processes, access to patients, access to trial sites and market potential. To chart the most important factors for clinical trial location choice, we scored the results of our survey in relative terms, zero indicating the relatively least important criteria compared to others.

Time and access to patients, followed closely by local expertise and quality of the trials conducted are the most important drivers of choice, while market potential is considered least important (Figure 20).

Approval timelines and access to patients are key drivers for location choice

With the pharmaceutical industry increasingly focused on achieving faster development times to counteract the increasing R&D cost pressures, it is not surprising that time is considered a key driver for clinical trial location choice. With respect to clinical trials, approval timelines include elements like approval time, time to initiate a site, patient recruitment speed and first patient, first visit.

Access to patients is equally considered a key driver for location choice. While patient population size, presence of specific patient populations and treatment-naive patients are important components, ease of access to patients by means of for instance specific recruitment tools or through patient organisations, is considered key.

Figure 20: Global drivers for clinical trial location choice

Source: PwC Survey 2012
Quality and expertise also greatly impact location choice

Expertise of site staff, competent authorities and ethics committees greatly impact the overall conduct, timelines and outcomes of clinical trials. Likewise, quality of trial execution and adherence to Good Clinical Practices are vital to the successful completion of a trial. Both quality and expertise are therefore considered important drivers for location choice.

Approval process and access to clinical trial sites are relatively less important drivers of location choice

When trying to effectuate cost savings and accelerating timelines, pharmaceutical companies attach importance to the predictability, transparency, and efficiency of clinical trial, ethics committee, and trial site processes. Access to trial sites includes the presence of specialised centres or hospitals with specific patient populations, transparency, and standardisation of trial costs and ease of contract negotiations.

Market potential is comparatively the least important driver of location choice

While market potential (potential return on investment, as measured by target population size, ease of market approval and access to reimbursement) is key to successful future capitalisation of R&D investments, it is comparatively less important compared to other drivers in terms of location choice.

Belgium is considered an attractive clinical trial location in terms of approval timelines, quality and expertise

The key driver for choosing Belgium as a clinical trial location – by far – is its favourable approval timelines (Figure 21). With an average competent authority approval time of 12 days for Phase I trials and 22 days for Phase II, III and IV trials, this is not surprising.

Belgium also scores well on local expertise of clinical trial staff and competent authorities, as well as quality of the clinical trial execution and Good Clinical Practice adherence.

CROs and pharmaceutical companies consistently commend Belgium for its presence of specialised centres offering specific knowledge and expertise as well as access to specific (often smaller/niche) patient populations through these centres.
Clinical trial costs and access to patients are restraining Belgium in attracting clinical trials

Two critical factors against Belgium are costs and access to patients, both key drivers in decision-making. Investigator fees and overhead cost charged by clinical trial sites are considered the most critical cost hurdle. There are teeming variations and lack of transparency in costs charged by different clinical trial sites. There are currently no national guidelines on costing in Belgium and both pharmaceutical companies and CROs fear this leads to imbalances.

While Belgium has a lot of patients on a relatively small surface area, they are not easily accessible, because they are distributed over different hospital sites. Companies experience difficulties with low referral rates, there are few tools available to assist them with patient recruitment (e.g. portals and databases) and there is a lack of strong patient organisations, which could help channel patients towards trials.
Stakeholder recommendations are pointing the way towards a more attractive clinical trial environment

To attract more clinical trials, Belgium needs standardisation and networking

When asked what changes would be needed for their organisation to be willing to allocate more clinical trials to Belgium in the future, all CROs and pharmaceutical companies surveyed indicate a high need for more standardisation in terms of processes (e.g. ethics committee processes, informed consent, site contracts etc.). This was followed closely by a need for closer networking and collaboration with and between individual clinical trials sites.

Mirroring the drivers against Belgium, an improved transparency in clinical trial costs is requested by 88% of respondents, with a call for “a cap on costs and clear cost calculation methods”.

A large majority (75%) further indicated a need for tools for recruitment such as patient registries to facilitate better referral and access to patients (Figure 22).

Figure 22: Changes needed for organisations to be willing to allocate more clinical trials to Belgium

"What changes are needed for your organisation to allocate more CTs to Belgium?"
Stakeholders point towards an environment that facilitates the execution of clinical trials

To arrive at a thorough understanding of how best to improve the Belgian clinical trial environment and attract more clinical trials, we asked each of the stakeholder groups to provide tangible recommendations to address current pain points in Belgium.

There was a high level of consistency in the recommendations issued. Recommendations could be categorised in 7 supporting pillars: network, processes, data and technology, training and education, legal and regulatory framework, resources and incentives (Figure 23).

Figure 23: Key categories of stakeholder recommendations

Unite researchers in expert networks

Building a collaborative research network of specialist expertise centres and public/private coordination hubs for clinical trials are recommended to overcome the smaller scale and scope of individual centres and to avoid fragmentation of competencies.

At the same time, networking can facilitate the pooling and sharing of expertise and transfer knowledge between centres in multi-centre studies. Such networks are also more convenient for pharmaceutical companies dealing with clinical trial centres and will improve the channelling of patients towards trials.

Simplify processes

A key theme throughout the survey was the need for standardisation, centralisation and harmonisation of key clinical trial processes like ethics committee approval, approval by competent authorities, or administrative processes in individual clinical trial sites. A single procedure with only one starting point and a seamless course throughout the clinical trial process could further enhance time to approval and address barriers like cost and access to patients.
Use data and technology to facilitate access to patients and information

Stakeholders recommend the construction of a national portal for clinical trials that contains a registry of patients, volunteers and clinical trials, much in the image of other countries like France and the United Kingdom. They envisage this portal as a gateway to all clinical trial processes containing a central trial submission point. Patient organisations specifically recommend using such technologies to publicise and disseminate information on which clinical trials are recruiting, as this will help channel patients.

Provide training and education

In order to further leverage the existing expertise and quality of clinical trials in Belgium, stakeholders recommend focusing on training and education at four levels: (1) clinical trial centres and their staff, (2) competent authorities and ethics committees, (3) physicians, patient organisations and patients and (4) the broader Belgian community.

By sharing best practices, standardising trainings, developing sound mechanisms for accreditation and raising the level of clinical trial know-how, clinical trial centres can strengthen their competitive reputation of quality and expertise.

Ethics committees and competent authorities are the key locusts of decision-making on clinical trial approvals. Ensuring training in relevant multi-disciplinary expertise (health economics, outcome measures, ethics, protocol assessment etc.) will further raise the bar in terms of approval times and their processes.

Raising awareness on clinical trials among physicians, patient organisations and patients will improve the channelling and guidance of patients in clinical trials. In this context it is important to draw the attention to benefits such as early access to innovative medicines and the regulatory frameworks that have been put in place to fully protect patients’ safety and interests.

As a nation, Belgium and its clinical trial centres can also invest in a stronger external branding of their clinical trial capabilities, positioning Belgium as a key clinical trial country on the global map.

Develop a supportive legal and regulatory framework

Stakeholders recommend several changes to the national and regulatory framework. These are most notably in the form of improved access to innovative medicines through more efficient approval processes, but also control or caps on clinical trial costs charged by investigational sites. Finally, to reduce local complexity, the EU regulatory framework should be translated to a local level with a minimum of redundancies or additional processes. Such initiatives will instil confidence in Belgium as a clinical trial location through improved transparency, flexibility and efficiency.

Allocate more resources to improve access to patients

Stakeholders stress the importance of adequate clinical trial resources and recommend focussing these resources on improving access to patients and on clinical trial centres specialising in key pathologies. This will enable faster identification and mobilisation of patients with specific diseases. Resources can be in the form of a key point of contact for clinical trials, the provision of experts on clinical trials, the provision of a patient registry, information and awareness campaigns etc.
**Provide incentives to foster collaboration and attract R&D**

To remain competitive, incentives for fostering collaboration are welcomed. Hospitals and physicians are often hesitant about referring patients to other clinical trial centres for fear of losing the patient permanently to the other centre. On top of this, sites competing to attract clinical trials form a barrier to proactive transparent collaboration. Incentives encouraging the exchanges between centres could help lower the barriers to collaboration and would facilitate the development of a Belgium-wide network of expertise centres. Tax incentives to further attract clinical trials and further funding and investments are also welcomed.

On the whole, this list of recommendations made by stakeholders to improve the local clinical trial environment is also applicable in a broader context of clinical research. They point the way forward in the formulation of a clear strategic plan to promote clinical trials in Belgium in particular, but also clinical research on a wider scale.
A strategic plan built on 3 key initiatives can promote clinical trials in Belgium

Future environment presents clear opportunities to boost clinical trials in Belgium

While the current pressures on the clinical trial environment are undoubtedly challenging, the future environment also presents clear opportunities. Belgium can leverage upon these opportunities to boost clinical trial activities.

First, the growing focus on evidence-based medicine is giving rise to a continuous process of data-gathering in clinical development and clinical practice. Already there is an increased demand for post-approval data-gathering and the current reimbursement process will likely shift towards a framework based on live licensing as described earlier in this report. This presents clear opportunities for smaller, faster, and more incremental trials for evidence-gathering.

The move towards stratified medicines will require a higher focus on translational research to drive discovery and development. Centres that can acquire expertise on new key evidence parameters, such as health economic data and capabilities in translational research and biobanking, will have a distinct advantage in this future environment.

While patient empowerment increases the pressure for a more transparent way of working, it also means patients are more willing to take on a proactive participating role in clinical trials. This can be leveraged upon to address a key barrier for Belgium in attracting clinical trials: access to patients. Patients will take more control and ownership of their treatments and actively seek out information and access to innovative medicines.

The European Commission is likely to adopt a revision of the Clinical Trials Directive 2001/20/EC later in 2012. The revision aims to streamline the clinical trial submission process, create a single submission portal and develop a mechanism of co-operation between Member States regarding clinical trial application. This new EU regulation will provide an opportunity to upgrade local expertise and at the same time, ameliorate the legal framework for biobanks, which will prove to be an instrumental partner to clinical trial centres in the future.

Finally, the trend towards more collaborative models of working, be it through licensing arrangements, public-private partnerships, outsourcing or co-development agreements, creates the right climate to develop larger and more intricate networks of clinical trial expertise centres. This in turn can help address several key clinical trials needs identified in Belgium, such as patient recruitment, standardisation and centralisation.
Three key strategic initiatives can help attract more clinical trials to Belgium

To improve the clinical trial environment in Belgium and attract more clinical trials, we propose a strategic framework based on three key strategic initiatives (Figure 24):

- a network of specialised centres;
- standardisation (‘one-stop shop’);
- a supportive governmental framework.

Figure 24: Strategic framework to promote clinical trials in Belgium

The first initiative involves the integration of clinical researchers in a network of specialised centres. Such a network would offer several distinct advantages. First, a network of specialised centres would further strengthen our attractiveness in terms of quality and expertise by avoiding fragmentation of competencies and enabling the pooling and sharing of best practices and key knowledge. Secondly, such a network would significantly improve access to patients, a key barrier for Belgium. It would facilitate consultation between the different specialised centres to locate and mobilise suitable patients and specific target groups of patients within specific pathologies.

Over time, this network could be linked more broadly with key partners like biobanks, which will play a key role in translational research, and the development of stratified medicines. This would facilitate biospecimen collection, analysis, storage and exchange, thereby generating efficiencies in time and cost.
A second initiative is a series of administrative simplifications through **standardisation and the setting-up of a ‘one-stop shop’**. The idea is to centralise both the competent authority and ethics committee approval processes in one key starting point in, for instance, an online portal for submission of trial applications. A second objective should be to standardise and harmonise all procedures and administrative tasks. This entails documents like informed consent forms and forms for negotiating contract agreements with clinical trial sites and investigators and should be made available to applicants through the portal. To complete the ‘one-stop-shop’ concept, the portal ought to be linked to a clinical trial registry indicating which trials are recruiting as well as a patient registry that can assist in the localisation of suitable trial participants. Such an initiative should ideally be governed by a public-private coordination hub.

When executed well, a ‘one-stop shop’ would significantly lower cost and time efforts, while improving transparency and access to patients and key information, thereby addressing several key barriers for Belgium.

The last initiative consists of the development of a **supportive governmental framework** that facilitates the access to innovative drugs (for instance through ‘live licensing’), caps the fees and costs that can be charged by investigators and clinical trial sites and provides more supportive incentives to the sector. Within this framework, the construct of a clinical trial and patient registry can be coordinated and guidelines towards standardisation and centralisation can be issued. This framework can then be extended to include clear standards, regulations and guidelines on biobanking. This is important as too many hurdles in biobanking regulations could lead to a further decrease in clinical trials in Belgium in the long term.

These three strategic initiatives combined will provide Belgium with a strong foothold to maintain and strengthen its position in the clinical trial market by addressing key barriers against Belgium as well as the individual stakeholder needs. At the same time, it will allow Belgium to anticipate the future environment and position itself as a leader ahead of other countries.

**Call for action to each of the different stakeholders**

To effectuate these three strategic initiatives, we propose the following key actions to each of the different clinical trial stakeholders.

**Pharmaceutical companies**

- Communicate clearly on the industry needs for standardisation and provide input on how a ‘one-stop-shop’ concept ought to be conceived.
- Focus on improving collaboration with clinical trial sites in their move towards a network of specialised centres.
- Liaise proactively with government to help shape policies towards a more supportive governmental framework for clinical trials.

**CROs, in- and outsourcing providers**

- On top of the actions formulated for pharmaceutical companies above, proactively communicate with pharmaceutical companies to identify service offerings that will enable more strategic alliances between both partners in the longer term.
National competent authorities

- Create a portal (linked to a clinical trial and patient registry) that can house a ‘one-stop shop’ which centralises and standardises clinical trial processes and administration.
- Coordinate the development of a network of specialised centres and develop suitable systems for accreditation of these centres and their clinical trial staff.
- Provide a supportive governmental framework that facilitates the control of costs and fees and enables access to innovative drugs.
- Provide certification and/or accreditation of investigators and ethics committees.

Hospital directions

- Collaborate more closely with other hospitals and clinical trial sites in order to evolve towards a network of more specialised centres.
- Focus on standardising and harmonising processes and forms across the network and provide clear and transparent cost calculations for clinical trials.
- Collaborate with the national authorities on the development of best-practice guidelines for clinical trial conduct, within the supportive governmental framework.
- Organise clinical trial infrastructure in the hospital, such as a dedicated clinical trial office or contact point.

Investigators/Academia

- Standardise fees charged to CROs and pharmaceutical companies for the conduct of clinical trials and communicate these clearly to CROs and pharmaceutical companies.
- Focus on developing disease-area specialty within a network of centres.
- Provide input to the government on the development of a clinical trial and patient registry.

Ethics committees

- Centralise the approval process across ethics committees, and progress towards a fully integrated, central ‘one-stop shop’ for ethics committee approval.
- Collaborate more closely with other ethics committees within the network to facilitate and enhance this centralisation.
- Collaborate with the national authorities on the development of best-practice guidelines for ethics review, within the supportive governmental framework.

Patient organisations

- Contribute to the development of a ‘one-stop-shop’ portal on clinical trials as a means to involve patients more in clinical trials, improve patient recruitment and raise awareness on opportunities for access to innovative medicines.
- Partner proactively with the centres within the network to provide input on opportunities for specialisation and to facilitate patient access.
• Liaise proactively with the government to help shape policies towards a more supportive governmental framework for clinical trials.

To improve the clinical trial environment in Belgium and attract more clinical trials, it is vital that each stakeholder group takes individual responsibility and appropriate action towards each of the three key strategic initiatives. When these changes are made in an open, collaborative manner, Belgium will be better placed to maintain and strengthen its position in the clinical trial market in the long term.
Appendix

Figure 25: Survey participants per stakeholder group

Figure 26: Key drivers for choosing Belgium (relative scale) – Subanaylsis for CROs

Source: PwC survey, 2012
Figure 27: Key drivers for choosing Belgium (relative scale) – Subanalysis for pharmaceutical companies

- Time to approval
- Presence of specialised centres
- Quality of CT execution
- Presence of expertise and skilled staff
- Transparency of approval processes
- Time to site initiation
- Time first patient first visit
- Patient recruitment speed
- Functioning of EC approval process
- Cost
- Participation rates
- Low participant drop-out rates
- Hospitals with access to large patient groups
- Patient population size

Source: PwC survey, 2012

Figure 28: Key deterrents against choosing Belgium (relative scale) – Subanalysis for CROs

- Cost
- Patient population size
- Patient recruitment speed
- Participation rates
- Time first patient first visit
- Time to approval
- Presence of specialised centres
- Hospitals with access to large patient groups
- Participant drop-out rates
- Presence of expertise and skilled staff
- Quality of CT execution
- Functioning of EC approval process
- Transparency of local regulatory approval process
- Time to site initiation

Source: PwC survey, 2012
Figure 29: Key deterrents against choosing Belgium (relative scale) – Subanalysis for pharmaceutical companies

Source: PhC survey, 2012
Table 1: Reported impact of further decline in clinical trials – per stakeholder group

<table>
<thead>
<tr>
<th>CROs, In- and Outsourcing Providers</th>
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<tbody>
<tr>
<td>Loss of jobs at all levels of the organisation</td>
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<td>Restructuring</td>
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<td>Shift to alternative core activities</td>
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<tr>
<th>Pharmaceutical Companies</th>
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<tbody>
<tr>
<td>Loss of jobs and closure of local clinical operations department</td>
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<tr>
<td>Loss of expertise (e.g. study management, R&amp;D in general)</td>
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<tr>
<td>Fewer Belgian experts in international decision bodies</td>
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<tr>
<td>Loss of innovation</td>
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<td>Decreased access to innovative treatments</td>
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<th>Health Authority</th>
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<td>Loss of budget</td>
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<td>Loss of expertise needed to provide early access to innovative treatments</td>
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<td>Loss of innovation</td>
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<th>Hospital Directions, Investigators and ethics committees</th>
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<tr>
<td>Closure of clinical trial units</td>
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<tr>
<td>Loss of jobs and budgets</td>
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<tr>
<td>Fewer publications</td>
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<tr>
<td>Decreased access to innovative treatments</td>
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<tr>
<td>Loss of innovation</td>
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<tr>
<td>Loss of knowledge and expertise</td>
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<th>Patient Organisations</th>
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<tbody>
<tr>
<td>Patients would no longer feel they were being taken seriously.</td>
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### Table 2: Stakeholders’ suggestions to make the clinical trial legal framework more attractive

<table>
<thead>
<tr>
<th><strong>CROs, In- and Outsourcing Providers</strong></th>
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<tbody>
<tr>
<td>• Develop a national template for informed consent forms.</td>
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<tr>
<td>• Standardise fees for clinical trial costs.</td>
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<tr>
<td>• Clarify safety reporting requirements.</td>
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<tr>
<th><strong>Pharmaceutical Companies</strong></th>
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<tbody>
<tr>
<td>• Develop a clear legal framework on standard of care.</td>
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<tr>
<td>• Standardise and simplify ethics committee process e.g. single submission, timeline adherence, alignment with EU Directive.</td>
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<tr>
<td>• Standardise and ensure transparency of costs structures.</td>
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<tr>
<td>• Standardise forms e.g. contracts and consent forms.</td>
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<tr>
<td>• Ensure there is no additional local legislation on top of EU legislation, e.g. no mandatory CAP.</td>
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<tr>
<td>• Improve access and reimbursement for innovative drugs.</td>
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<tr>
<td>• Simplify regulations in non-interventional trials.</td>
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<th><strong>Health Authority</strong></th>
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<tbody>
<tr>
<td>• Benchmark.</td>
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<tr>
<td>• Thoroughly revise current framework i.f.o. the revised EU Directive.</td>
<td></td>
</tr>
<tr>
<td>• Effect legal changes on the role of ethics committee.</td>
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<thead>
<tr>
<th><strong>Hospital Directions</strong></th>
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<tr>
<td>• Ensure short timelines.</td>
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<tr>
<td>• Centralise the organisation of clinical trials.</td>
<td></td>
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<tr>
<td>• Create accreditation and certification of site and staff.</td>
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<tr>
<td>• Improve informed consent form.</td>
<td></td>
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<tr>
<td>• Clearly define possible sponsors of investigator-driven trials.</td>
<td></td>
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<tr>
<td>• Standardise insurance/liability.</td>
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</table>
**Table 3: Anticipated changes in the clinical trial landscape for 2012-2017 – per stakeholder group**

**CROs**

<table>
<thead>
<tr>
<th>Exploratory Trials</th>
<th>Confirmatory Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Globalisation of processes and structures</td>
<td>• Globalisation of processes and structures</td>
</tr>
<tr>
<td>• Increased competition from phase I units (also in emerging and BRIC countries)</td>
<td>• Increased use of freelancers and subcontractors to avoid challenges of fixed headcounts</td>
</tr>
<tr>
<td>• More multi-centre, international, combined trials covering FIH to POC</td>
<td>• Increased need for creative approaches to performing clinical trials to meet changing regulatory requirements</td>
</tr>
<tr>
<td>• More use of freelancing</td>
<td></td>
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</tbody>
</table>

**In- and Outsourcing Providers**

<table>
<thead>
<tr>
<th>Exploratory Trials</th>
<th>Confirmatory Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Increased complexity (tailor-made projects, speciality projects)</td>
<td>• Local implementation problems in global contract deals</td>
</tr>
<tr>
<td>• Loss of visibility, profit and commitment due to a need to work in subcontract for CROs</td>
<td>• Loss of visibility, profit and commitment due to a need to work in subcontract for CROs</td>
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</table>

**Pharmaceutical Companies**

<table>
<thead>
<tr>
<th>Exploratory Trials</th>
<th>Confirmatory Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Shift towards emerging markets</td>
<td>• Shift towards emerging markets</td>
</tr>
<tr>
<td>• Increased outsourcing (except eCTA studies)</td>
<td>• Increased outsourcing of full studies</td>
</tr>
<tr>
<td>• Increased insourcing due to headcount freezes (e.g. data management, monitoring)</td>
<td>• Increased insourcing due to headcount freezes</td>
</tr>
</tbody>
</table>
Table 4: Stakeholders’ suggestions on how to improve the Belgian clinical trial landscape

<table>
<thead>
<tr>
<th>CROs, In- and Outsourcing Providers</th>
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<tbody>
<tr>
<td>• Standardisation e.g. informed consent requirements, costs, processes, contract templates</td>
</tr>
<tr>
<td>• Professionalisation e.g. upgrade of the minimal scientific level required to become a clinical trial professional</td>
</tr>
<tr>
<td>• Centralisation e.g. one central ethics committee</td>
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<tr>
<td>• Clear guidelines on standard of care</td>
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<tr>
<td>• Reduction of administrative burden</td>
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<tr>
<td>• Availability of tools e.g. for patient recruitment</td>
</tr>
<tr>
<td>• Adherence to timelines</td>
</tr>
<tr>
<td>• Encouragement of the viability of local CROs and outsourcing agencies that have local knowledge</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pharmaceutical Companies</th>
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</thead>
<tbody>
<tr>
<td>• Standardisation e.g. ethical committee processes and requirements, costs</td>
</tr>
<tr>
<td>• Professionalisation e.g. increased competency of ethics committees, pharmacovigilance experts</td>
</tr>
<tr>
<td>• Centralisation e.g. one central, independent ethics committee, central point of access for clinical trials</td>
</tr>
<tr>
<td>• Specialisation e.g. increased expertise in specialised clinical trial studies</td>
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<tr>
<td>• Clear guidelines on standard of care</td>
</tr>
<tr>
<td>• Set-up of expertise sites that can act as referral sites for clinical trials</td>
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<tr>
<td>• Improvement of visibility of ongoing trials towards patients and physicians</td>
</tr>
<tr>
<td>• Adherence to timelines</td>
</tr>
<tr>
<td>• Incentives for R&amp;D</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Hospital Directions</th>
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</thead>
<tbody>
<tr>
<td>• Standardisation e.g. cost structures, contracts, informed consent forms, processes, ethics process</td>
</tr>
<tr>
<td>• Centralisation e.g. reduction of number of ethics committees</td>
</tr>
<tr>
<td>• More cooperation and harmonisation e.g. between universities</td>
</tr>
<tr>
<td>• Accreditation of clinical trial centres</td>
</tr>
<tr>
<td>• Clear SAE reporting procedures</td>
</tr>
<tr>
<td>• Pragmatic approaches to GMP inspections</td>
</tr>
</tbody>
</table>
Table 5: Priority actions proposed by stakeholders on key clinical trial needs

**Actions towards improving patient recruitment**
- Improve image of clinical trials towards patients (e.g. patient flyers).
- Increase collaboration between clinical trial centres.
- Create a Belgian trial registry.
- Create one central portal for clinical trials.

**Actions towards improving access to information on clinical trials**
- Provide objective and comprehensible information to patients and physicians.
- Publicise trial information on a national level.
- Leverage the FAMHP website.

**Actions towards standardisation**
- Assign a mandate to government authority to make legally binding proposals towards standardisation.
- Coordinate initiatives between research centres on a Belgian and European level.
- Make available standard templates (e.g. agreements, informed consent).
- Develop certification for ethics committees and create common SOPs.
- Build INAMI guidelines.

**Actions towards improving the ethics committee process**
- Clarify roles and responsibilities.
- Work towards European guidelines for the evaluation process.
- Reduce the number of Belgian ethics committees (e.g. 1 single one).
- Standardise and harmonise applications.

**Actions towards increasing transparency in clinical trial costs**
- Set up a national study board (incl. doctors, INAMI, mutualities and pharmaceutical companies) to develop guidelines/policies on cost.
- Standardise investigator fees.
- Publish costs.
- Stimulate closer cooperation between clinical trial centres.
- Develop a single financial contract agreement.

**Actions towards increasing efficiency of clinical trial processes**
- Stimulate collaboration between clinical trial units.
- Professionalise ethics committees and clinical trial centres.
- Train and educate investigators.
- Centralise the processes and standardise the forms.

**Actions to improve networking**
- Develop a central interactive website for all key stakeholders.
- Decrease negative competition drivers (e.g. publication quota).
- Stimulate and incentivise the exchange of information.
- Initiate common projects.
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