ACQAS

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Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

Capacity and Capability Analysis of the Clinical Trial Units at the Belgian University hospitals

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Capacity and Capability Analysis of the Clinical Trial Units at the Belgian University hospitals

Candidate Sponsors under review	CU Saint Luc UZ Leuven UZ Gent CHU Liège UZA UZ Brussel Hôpital Erasme
Visit dates	Between 2 May and 14 September 2016

1. Purpose and scope

The assessment of sponsor capacity at universities and hospitals in Belgium is part of the KCE Trials Programme, a publicly funded programme of pragmatic practice-oriented trials, to build a network of clinical trial units which can take up the function of a clinical trial sponsor. The initial focus was the 7 main university hospitals since they are the most likely candidate sponsors for the clinical trials financed by KCE under this programme.

The scope and focus of the visits was compliance with ICH-GCP and ISO 9001, in particular the sponsor processes necessary to be able to initiate, execute, manage and oversee multicentre, pragmatic, comparative effectiveness studies, including but not limited to:

- Overall Management System: Quality Policy/Manual, Organogram, set-up of studies
- Selection of sponsor staff involved in the management and oversight of study conduct (e.g., protocol development, Clinical Operations, Randomisation, Data Management, Pharmacovigilance (PV), Clinical Supplies, Biostatistics, System Support), and relevant training
- Document Management Processes
- Quality Processes, including audits, non-conformance/CAPA management, process improvement, Quality Management Reviews
- Study design, performance, analysis and reporting including, protocol development and medical oversight
- Site Selection and Oversight Process
- Contracting and Sub-contracting Process
- IMP management and accountability Process
- Central Lab management and Reporting Process
- Infrastructure and IT Processes

The following visits were performed:

1. CU Saint-Luc on 3 – 4 May 2016
2. UZ Leuven on 25 – 26 May 2016
3. UZ Gent on 1 – 2 June 2016
4. CHU Liège on 29 – 30 June 2016
5. UZA on 11 – 12 August 2016
6. UZ Brussels 18 – 19 August 2016
7. Hôpital Erasme13 – 14 September 2016

2. Overall Summary

The overall outcome is summarised in the overall risk summary section.

Areas of compliance:

The two areas where all university hospitals were compliant with meeting the sponsor requirements for managing pragmatic multicentre randomised trials were for adequate sponsor insurance and supporting Central Laboratory Processes.

Areas of minor concerns (overall ≤ 3 majors)
For the following areas the university hospitals were either compliant or minor/a few major risks were identified:

- All hospitals showed a commitment to develop a central clinical trial unit in support of sponsor required processes. Overall, there was commitment and support from the general management (4 compliant, 3 minor)
- The overall organisation present at the university hospitals had the potential for meeting the capacity and the capabilities for managing pragmatic multicentre randomised trials (1 compliant, 5 minor, 1 major)
- All university hospitals had centralised submission processes in place that could cope with multicentre studies (4 compliant, 3 minor)
- All hospitals, except one, had robust Clinical Supplies facilities and processes in place to be able to cope (or outsource) with sponsor management of clinical supplies in multicentre randomised studies (6 compliant, 1 major)
- All university hospitals had the required infrastructure and IT support systems in place required to support the necessary sponsor processes (5 compliant, 2 minor)
- All hospitals, except one, had the necessary regulatory knowledge in place to meet the regulatory requirements of acting as sponsor for multicentre randomised studies (5 compliant, 1 minor, 1 major)
- All university hospitals had Trial Master File documentation and archiving processing in place, but this was mostly not supported by procedures or where present the archiving facilities/procedures needed to maintain and archive essential documents were inadequate. The same was applicable for protocol development: all hospitals knew how to develop protocols, but this was not described in a supporting procedure and a review/approval process was not in place (all minor).
- All except two university hospitals could show extensive experience (> 10 trials) in managing multicentre randomised studies. It must be noted that this experience was spread throughout the different departments and not centralised (5 minor, 2 major)
- All university hospitals, except two, had a document management system in place, with procedures and (non-mandatory) training for relevant staff. The observation in general was that not all documents, processes in place were supported by appropriate procedures (5 minor, 2 major).
- Four out of seven university hospitals had an auditing group in place but the audits performed were not particularly (or not) focusing on those processes that are elementary to be able to function as a sponsor (4 minor, 3 major).
- All university hospitals, except two, had biostatisticians or could rely on biostatisticians from the university they were liaised with to support the clinical trials but either the processes in place were not supported by procedures or the support was ad hoc (departmental knowledge rather than centralised knowledge). In addition, centralised processes to assist investigators with designing protocols and statistical plans, and reviewing clinical study reports/publications were not in place. (5 minor, 2 major).
- The major risk concerning training in sponsor specific tasks and responsibilities was that it was not mandatory for any of the university hospitals and it was not appropriately tracked to ensure that employees were trained before they could perform any sponsor related task. It was also not clear to most hospitals that taking on sponsor responsibilities entailed more than just GCP training (which was mostly focused on investigator responsibilities and not sponsor responsibilities) (5 minor, 2 major)

Areas of major concerns (overall > 3 majors)
For the following areas at least 4 Universities had major risks identified:

- Quality Management System (QMS): None of the university hospitals visited had a compliant Sponsor Quality Management System in place which was to be expected since this initiative is new to Belgium and still needs to be expanded. Overall, there was very little centralisation in place, and as such centralised sponsor oversight processes (e.g. Pharmacovigilance, Quality Management - including audits, CAPA and process improvement management, Document Management, essential document management, etc) were lacking or not robust enough yet. One university hospital had already invested a lot of effort and was quite advanced to have a compliant QMS in place (6 major, 1 minor).
- None of the university hospitals had adequate processes in place to manage non-compliance, GCP breaches and CAPAs (all major).
- Site selection and oversight processes were either not robust enough or not well documented. Most university hospitals & their individual departments had plenty of experience of taking part in commercial clinical trials and being overseen by the sponsor companies but there was little overall experience in having a good site selection and oversight process as sponsor in place (4 major, 3 minor).
- Site recruitment and oversight were overall not adequate for the same reason as site selection (see above) (4 major, 3 minor).
- Data management processes were either not fully implemented or inadequate (4 major, 3 minor).
- Pharmacovigilance processes were inadequate because most university hospitals did not have the sponsor required oversight processes for safety management in place (6 major, 1 minor).
- Because none of the university hospitals had a robust sponsor oversight system in place, an important part of sponsor oversight, i.e. Vendor Management, had not yet been implemented. If it was, it was not documented and supported by appropriate procedures (all major).

3. Overall Conclusions

None of the university hospitals assessed fully met all sponsor process requirements, which was to be expected given that these type of studies, i.e. university hospitals acting as sponsor for pragmatic, multicentre randomised trials, is fairly new to Belgium. All university hospitals had made efforts to initiate and support these types of processes and at least one university hospital had already made considerable progress to meet all the requirements, while others were still in the process of setting up an adequate system.

Since some university hospitals have already invested extensively in certain processes (e.g. document management, eCRF, site oversight, and central clinical trial centre) it is advised that these processes are leveraged from and discussed at a cross-university platform. It would also be advisable that in case certain systems/platforms are developed (e.g. eCRF) that these are discussed across university hospital level and that a minimum of platforms are implemented (and available) at all university hospitals to bring consensus and uniformity in this type of studies. Cooperation and discussion between the different centres will become central to the success for the KCE project.

It is also advised that KCE provides further expectations, advice and guidelines to support the conduct of pragmatic, randomised multicentre trials in Belgium and internationally.

4. Definitions

Risk grading

Compliant:	Requirement fully documented and implemented. Process compliant with the standard or specification
Minor risk:	Minor gap, requirement is mostly documented and implemented. The process may be weak, cumbersome, redundant, overly complex, or in some other manner, needs improvement. Requirement has been implemented but only partial documentation available
Major risk:	Requirement has been implemented but not documented, or documented but not implemented. A non-conformity that, based on the evidence, is not likely to result in the failure of the process or reduce its ability to assure controlled processes. It may be either a failure in some part of the process relative to a specified requirement or a single observed lapse in following one item of an organisation's management system. A number of minor non-conformities against one requirement can jeopardise the process and thus be considered a major observation.
Critical risk:	No provision, requirement not documented or implemented. The absence (omission, not addressed) or total breakdown (omission, failure, not implemented) of a process to meet a specified requirement. A number of major non-conformities against one requirement can represent a total breakdown of the process and thus be considered a critical observation. This includes conditions that may result in the failure of or materially reduce the usability of products or services for their intended purpose. A non-compliance that, in the judgment and experience of the auditor, is likely either to result in the failure of the management system or to materially reduce its ability to assure controlled processes and products.
Recommendation:	No critical major or minor non-conformances found, but there is an opportunity to improve the current status of the process

Overall Grading Level (OGL):

As no grading exists regarding the evaluation of sponsor capacity for non-commercial trials, the following grading score was developed based on an algorithm to provide a consistent and robust grading score

First, the overall Grading Score is calculated:

Number of Critical Risks x 25 = A

Number of Major Risks x 5 = B

Number of Minor Risks x 2 = C

A + B + C = Overall Grading Score (OGS)

Overall Grading Score	Overall Grading Level
>=100	OGL-1
60-99	OGL-2
20-59	OGL-3
1-19	OGL-4
0	OGL-5

OGL-1: Overall seriously deficient processes, risks were observed that may be a major threat to subjects' safety, scientific validity, data integrity or process integrity or to KCE's business interests. The deficiencies are probably not correctable and may invalidate the data or process. Immediate action is required. In the current state it is inadvisable/too great a risk to fund the organisation to be considered as sponsor for KCE funded trials.

OGL-2: Overall major risks that may impact subjects' safety, scientific validity, data integrity or process integrity, or KCE's business interests were observed which will require intensive follow-up or may not be correctable. The integrity of a study or process may be affected. Prompt action is required before the organisation can be considered as sponsor for KCE funded trials.

OGL-3: Overall moderate risks that may impact subjects' safety, scientific validity, data integrity or process integrity, or KCE's business interests were observed which will require follow-up. The deficiencies should not affect the integrity of the study or process. Action is recommended for the organisation to be considered as sponsor for KCE funded trials.

OGL-4: Overall, minor risks that may impact subjects' safety, scientific validity, data integrity or process integrity, or KCE's business interests were observed. The deficiencies will not affect the integrity of the study or process. Process improvement actions may be considered but this will not impact the organisation to be considered as sponsor for KCE funded trials.

OGL-5: Overall compliance. Action or follow-up is not required. Organisation meets all requirements to be considered as sponsor for KCE funded trials

Date of final report: 24 October 2016

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5. Overall Risk Summary Section

Area reviewed	Risk Rating	Risk Rating	Risk Rating	Risk Rating	Risk Rating	Risk Rating	Risk Rating
1. Sponsor Organisation and Management	I Score : 53 Grade 3	II Score : 40 Grade 3	III Score : 56 Grade 3	IV Score : 55 Grade 3	V Score : 48 Grade 3	VI Score : 95 Grade 2	VII Score : 61 Grade 2
1.1.Organisation	Minor	Compliant	Minor	Minor	Minor	Major	Minor
1.2. Management Oversight	Compliant	Compliant	Minor	Compliant	Compliant	Minor	Minor
1.3 QMS	Major	Major	Major	Minor	Major	Major	Major
1.4. Document Management Process	Minor	Minor	Major	Minor	Minor	Major	Minor
1.5. Staff and training	Minor	Minor	Major	Major	Minor	Minor	Minor
1.6. Regulatory knowledge	Minor	Compliant	Compliant	Compliant	Compliant	Major	Compliant
1.7. Quality Assurance and auditing processes	Major	Minor	Minor	Minor	Minor	Major	Major
1.8. Non-compliance and CAPA management	Major	Major	*Major*	Major	Major	Major	Major

Area reviewed	Risk Rating	Risk Rating	Risk Rating	Risk Rating	Risk Rating	Risk Rating	Risk Rating
2. **Infrastructure for Clinical Research**							
2.1. Multi-centre Clinical Trials	Minor	Minor	Minor	Minor	Minor	Major	Major
2.2. Protocol development	Minor	Minor	Minor	Minor	Major	Minor	Minor
2.3. Sponsor Insurance	Compliant	Compliant	Compliant	Compliant	Compliant	Compliant	Compliant
2.4. Site selection and oversight	Major	Minor	Minor	Minor	Major	Major	Major
2.5. Vendor Management	Major	Major	Major	Major	Major	Major	Major
2.6. Recruitment Strategy, tracker, status reports and oversight	Major	Minor	Minor	Minor	Major	Major	Major
2.7. Trial Master File process, documentation and archiving	Minor	Minor	Minor	Minor	Minor	Minor	Minor
2.8. Data management processes	Minor	Minor	Major	Major	Minor	Major	Major
2.9 Pharmacovigilance processes	Major	Major	Major	Major	Minor	Major	Major
2.10. Biostatistics and reporting processes	Minor	Minor	Major	Major	Minor	Minor	Minor
2.11. Regulatory submission processes	Compliant	Compliant	Compliant	Minor	Compliant	Minor	Minor
2.12. Clinical Supplies processes	Compliant	Compliant	Compliant	Major	Compliant	Compliant	Compliant
2.13.Central laboratory processes	Compliant	Compliant	Compliant	Compliant	Compliant	Compliant	Compliant
3. **Infrastructure and IT support**							
3.1. Information Systems	Compliant	Compliant	Compliant	Compliant	Compliant	Minor	Minor