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Danish Health and Medicines Authority

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ANNUAL REPORT 2014

Clinical trials of medicines

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Axel Heides Gade 1
2300 Copenhagen S
Denmark
dhma.dk

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SUMMARY

Marginal decrease in the number of clinical trial applications in 2014 on 2013

In 2014, the Danish Health and Medicines Authority (DHMA) received 284 applications for authorisation of clinical trials of medicines in humans, which is a fall of 3% on 2013. Commercial sponsors applied for 162 trials and researchers (non-commercial sponsors) for 122. It is positive that the level is comparable to 2013, when the number increased by 14%, and that the development in the number of trials since 2010 has been successfully reversed. The decrease may be explained by a lower number of applications for phase I trials.

Decline in the number of trial subjects

In 2014, 13,743 Danish trial subjects are expected to participate in 284 trials. This is a reduction of around 3,000 compared to 2013 (16,882). This is a decline of 19% on 2013. The average number of trial subjects per clinical trial dropped from 57 in 2013 to 48 in 2014. This downward trend can be traced back to 2011, when the average number of trial subjects was 76. The primary reason for the decline is that we have not received any applications for trials with more than 500 trial subjects.

Cancer is the dominant therapeutic area

Cancer-related trials account for 28% of all trial applications and 20% of all trial subjects.

Continued rise in the share of multinational trials

The share of multinational trials is increasing and accounts for 65% of all trial applications, and the number of national trials is declining. This underlines how important it is that the Danish authorities participate actively in influencing the European development in this area.

The annual report presents several data on trials notified in 2014, and the preparations for the new European legislation (Clinical Trials Regulation 536/2014) is also described.

2

MARGINAL DECREASE IN THE NUMBER OF CLINICAL TRIAL APPLICATIONS IN 2014 ON 2013

In 2014, DHMA received 284 applications for authorisation of clinical trials of medicines in humans, which is a fall of 3% on 2013.

Commercial sponsors applied for 162 trials and researchers (non-commercial sponsors) for 122.

Number of clinical trials notified to DHMA			
Year	**Commercial sponsor**	**Non-commercial sponsor**	**Total**
2005	215	89	304
2006	229	107	336
2007	207	63	270
2008	194	81	275
2009	183	85	268
2010	142	84	226
2011	154	117	271
2012	153	106	259
2013	165	129	294
2014	162	122	284

Table 1: Number of clinical trial applications received from 2005 to 2014, by type of sponsor.

It is positive that the level is comparable to 2013, when the number increased by 14%, and that the development in the number of trials since 2010 has been successfully reversed.

The number of applications from non-commercial sponsors dropped by 7, or 6% relative to 2013. In the same period, the number of applications from commercial sponsors dropped by 3, or 2%. The percentage distribution of applications from commercial and non-commercial sponsors, respectively, in 2014 (57% and 43%) is comparable to the figures from 2013 (56% and 44%).

Appendix 1 shows a graphical presentation of the development in the number of clinical trial applications by type of sponsor from 2006 to 2014.

Table 2 shows that the cancer field (neoplasms benign, malignant and unspecified (incl cysts and polyps)) continues to be the most frequent therapeutic area among clinical trial applications. This has been the case for four years. The number of applications related to cancer declined from 86 applications in 2013 to 80 in 2014. The number of applications related to cancer is almost four times higher than the four second-most occurring therapeutic areas. Compared with 2013, nervous system disorders and cardiac disorders are no longer in top five of the most frequent therapeutic areas within clinical trials. Clinical trials in congenital, familial and genetic disorders increased from 8 in 2013 to 19 in 2014. Trials within the broad designation of investigations, including pharmacokinetics studies, also increased from 11 to 22 trials.

Appendix 2 shows the distribution of all clinical trial applications by therapeutic area (blue bars).

Notified trials by therapeutic area	
MedDRA[1] therapeutic area code	**Number of trials**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	80
Investigations	22
Surgical and medical procedures	21
Congenital, familial and genetic disorders	19
Metabolism and nutrition disorders	18

Table 2: Top 5 therapeutic areas measured by number of clinical trial applications in 2014.

3

FALL IN THE NUMBER OF TRIAL SUBJECTS

In 2014, 13,743 Danish trial subjects are expected to participate in 284 trials. This is a reduction of around 3,000 compared to 2013 (16,882). This is a decline of 19% on 2013. The average number of trial subjects per clinical trial dropped from 57 in 2013 to 48 in 2014. This downward trend can be traced back to 2011, when the average number of trial subjects was 76.

Figure 1 shows the number of clinical trials in trial subject ranges. Compared to the values from 2013, the number of trials with more than 500 trial subjects declined from 5 to zero in 2014, and this is the primary reason for the major fall in the total number of trial subjects. At the same time, the number of trials with less than five trial subjects increased from 12 in 2013 to 17 in 2014. The lowest number of trial subjects in 2014 was one, the highest 440.

[1] Medical Dictionary of Regulatory Activities

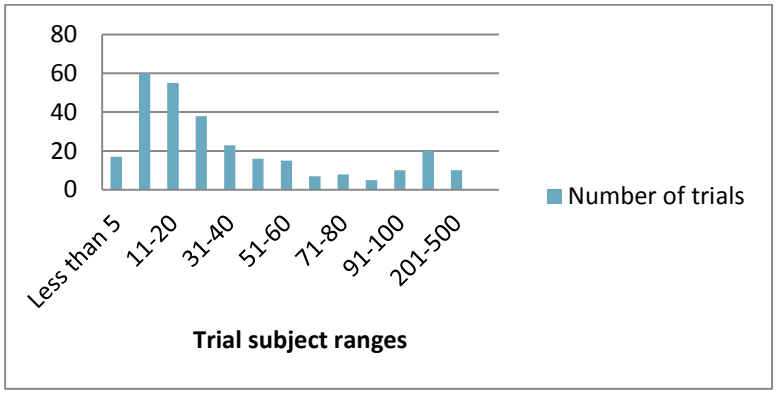

Figure 1: Bar chart of the number of trials in trial subject ranges.

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MOST TRIAL SUBJECTS IN TRIALS DEALING WITH CANCER

The therapeutic areas with the highest number of clinical trial subjects appear from table 3. Compared with data from 2013, the number of trial subjects in trials dealing with cardiac disorders fell from 3,541 to 1,142 in 2014, whereas the number of trial subjects in trials dealing with cancer increased from 2,025 to 2,914 in the same period.

Appendix 2 shows the distribution of trial subjects on therapeutic areas (yellow bars).

Top 5 therapeutic areas measured by number of trial subjects	
MedDRA therapeutic area code	**Number of trial subjects**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2,914
Surgical and medical procedures	2,445
Cardiac disorders	1,142
Metabolism and nutrition disorders	1,023
Infections and infestations	922

Table 3: Top 5 therapeutic areas measured by number of trial subjects.

5
INCREASING SHARE OF MULTINATIONAL TRIALS

Among the 284 trials, 184 (65%) trials are conducted simultaneously in Denmark and other European countries, whereas just over one third of the trials (100) are conducted in Denmark only.

Among the 100 national trials, 90% (90) of the trials are conducted by non-commercial sponsors, and only 10% (10) are conducted by commercial sponsors. Among the 184 multinational trials, 82% (152) of the trials are conducted by commercial sponsors, and 18% (32) are conducted by non-commercial sponsors. Among the 162 commercial trials, 10 trials are conducted nationally, corresponding to 6% of all commercial trials. Among the 122 non-commercial trials (122), 90 trials are conducted in Denmark only, corresponding to 74% of the total number of non-commercial trials.

Table 4 shows that the share of multinational trials is increasing, whereas the share of national trials is decreasing. This observation is in line with previous annual reports and underlines how important it is that the Danish authorities continue to participate actively in influencing the European development in this area.

Distribution of multinational and national trials by type of sponsor						
	Multinational trials			**National trials**		
	Commercial	Non-commercial	All trials	Commercial	Non-commercial	All trials
2011	144	26	170	10	91	101
2012	144	16	160	9	90	99
2013	148	29	177	17	100	117
2014	152	32	184	10	90	100

Table 4. Distribution of multinational and national trials by type of sponsor from 2011 to 2014.

6

FEWER PHASE 1 APPLICATIONS MAY EXPLAIN THE MARGINAL DECREASE IN CLINICAL TRIAL APPLICATIONS

Figure 2 shows the distribution of applications according to trial phase and type of sponsor from 2011 to 2014. It appears from the figure that the marginal decrease in the number of applications from 2013 to 2014 is mainly attributable to the decline in the number of phase I applications. The number of clinical trial applications in phases II, III and IV are comparable with data from 2013.

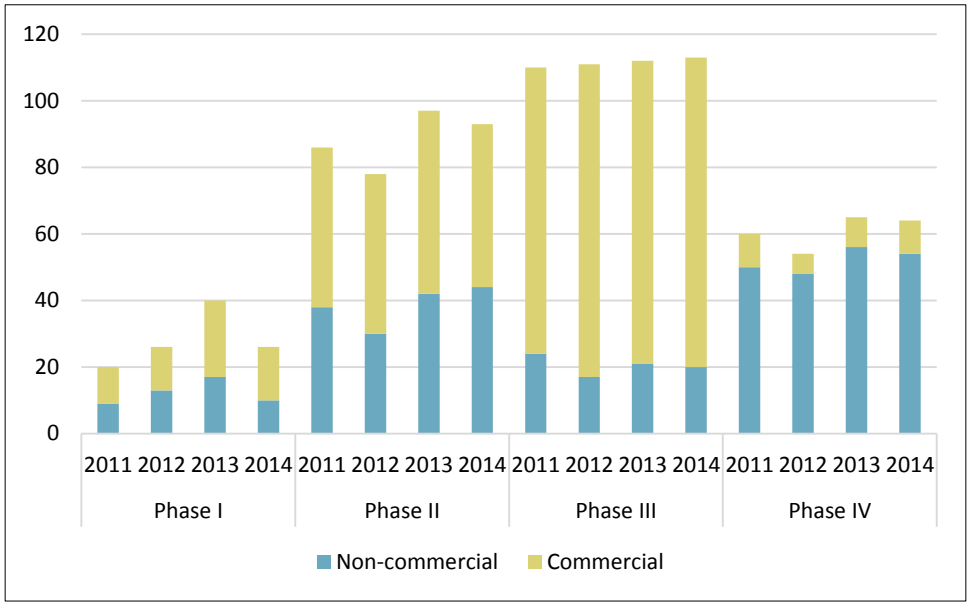

Figure 2: Distribution of clinical trial applications according to trial phase and type of sponsor.

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INCREASE IN THE NUMBER OF CLINICAL TRIALS COORDINATED BY THE CAPITAL REGION OF DENMARK

Figure 3 shows the distribution of clinical trial applications according to which regional ethics committee has received the application for approval. The Capital Region of Denmark coordinates the vast majority of clinical trial applications, and the number increased to 62% in 2014 against 56% in 2013. The increase is the result of a rise in commercial applications (76 applications against 66 in 2013), whereas the number of non-commercial applications is at the same level as last year (100). Fewer clinical trials are coordinated by Central Denmark Region, which saw a fall of 23 clinical trial applications from 66 in 2013 to 43 in 2014. The number of applications from commercial sponsors fell by 11, and from non-commercial sponsors by 12. The number of clinical trials coordinated by Region Zealand doubled from 4 in 2013 to 9 in 2014. The other regions coordinate more or less

the same number of applications as in 2013. Region of Southern Denmark received 44 applications (37 in 2013), and North Denmark Region received 12 (11 in 2013).

In this connection it is important to bear in mind that an authorised clinical trial of medicinal products which is coordinated from the Capital Region of Denmark may be conducted at clinical departments (sites) in hospitals of other Danish regions. Consequently, the figure does not point to trends for the overall clinical research activity with medicines in a specific region.

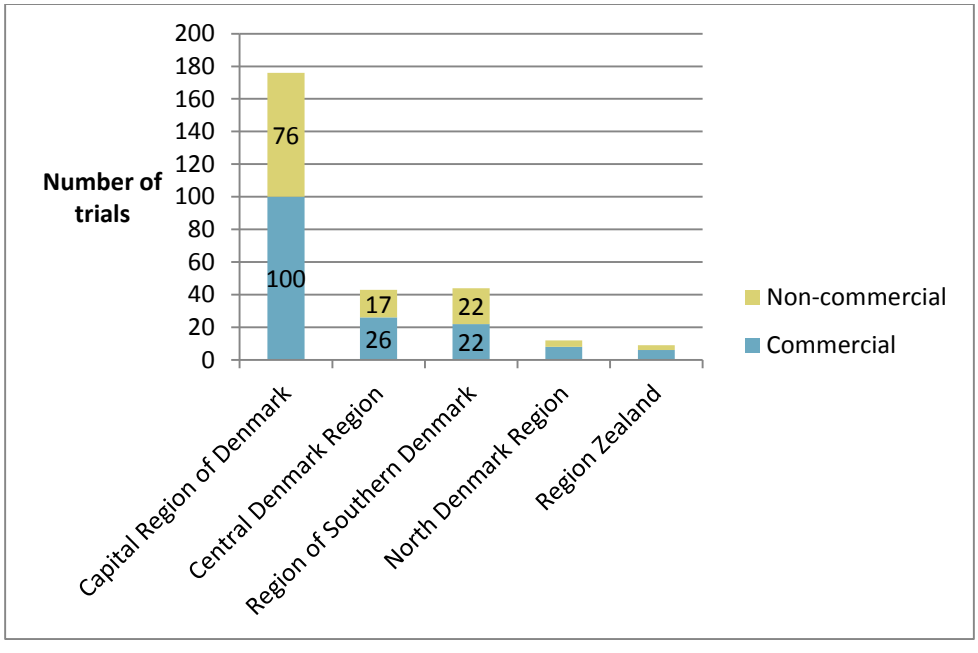

Figure 3: Distribution of clinical trial applications according to type of sponsor and regional affiliation of the ethics committee with which the application has been filed.

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ASSESSMENT BY DHMA

The work with clinical trials is organised in the Clinical Trials Unit under Medicines Licensing & Availability. The Clinical Trials Unit has nine full-time and ten part-time employees. The unit reviews clinical trial applications and monitors all ongoing trials based on notified amendments, reported adverse reactions and annual safety reports.

DHMA received 284 applications in 2014. We granted 278 authorisations, refused 4 applications and withdrew 2 trials.

Stable use of Voluntary Harmonisation Procedure

Since 2009, it has been possible to obtain a coordinated assessment of an application for a clinical trial that is to take place in more than three European countries through the Voluntary Harmonisation Procedure (VHP). Figure 4 shows that the number of cases being reviewed through this procedure is comparable with 2013. Denmark participated in 45 cases, which implies that 24% of the authorisations for the conduct of multinational clinical trials in Denmark were coordinated with the other regulatory authorities in the EU. Denmark's share of the total number of European VHP cases is 26%. Denmark acted as reference member state in 1 case in 2011, 2 cases in 2012, 5 cases in 2013 and 1 case in 2014.

The procedure is offered by the European working group Clinical Trials Facilitation Group (CTFG). CTFG was formed by the Heads of Medicines Agencies in 2004 with the purpose of coordinating and seeking harmonisation of decisions and administrative procedures related to the GCP Directive 2001/20/EC, which came into force in 2004. Read more about the procedure.

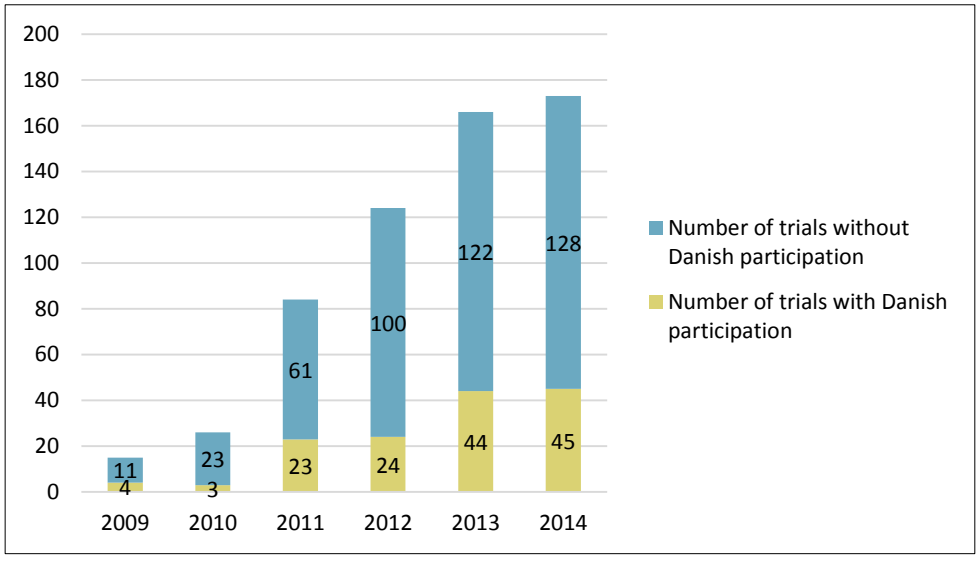

Figure 4: Number of cases reviewed through the VHP

Assessment times

The maximum time for assessment is 60 calendar days[2] as set out in the executive order on clinical trials of medicinal products in humans. If DHMA gives grounds for non-acceptance, the sponsor can amend the application once. To ensure that the sponsor has the required time to amend the application, it has been agreed with the pharmaceutical industry that the sponsor is to receive a reply within 42 calendar days, starting on the day DHMA has received a duly completed application.

In 2014, 91% of all applicants received a reply within 42 calendar days. 9 % received a reply within 60 calendar days and the remaining <1% received replies after more than 60 calendar days.

Our assessment times are published regularly on our website. In 2013, 88% of all applications were replied to within 42 calendar days. In light of the resources allocated, the assessment times are considered satisfactory.

[2] The deadline is extended by 30 calendar days for the review of applications for trials with medicines for gene therapy and somatic cell therapy and medicines containing genetically modified organisms. For these medicines, the deadline of 90 days may be extended by a further 90 days in cases where public boards or the like are consulted.

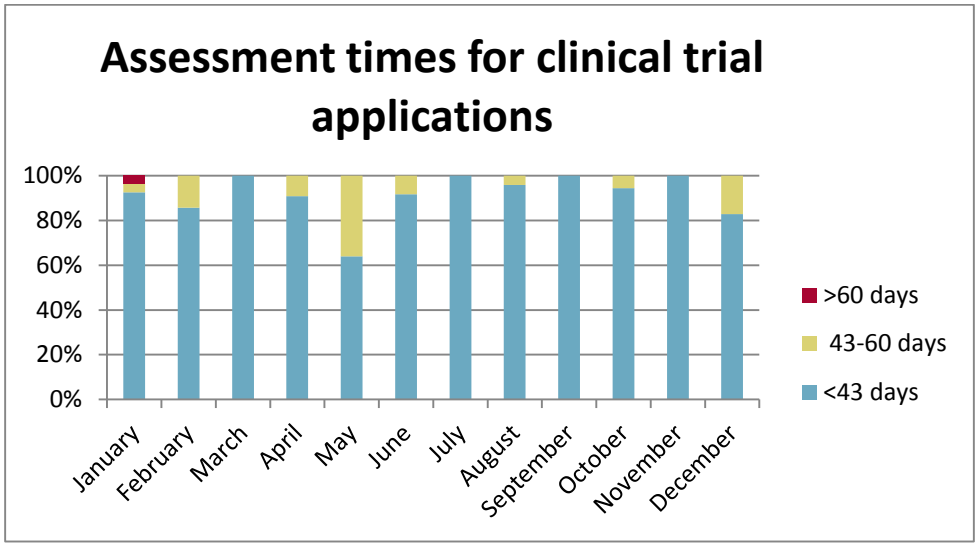

Figure 5: Assessment time intervals as a percentage of the total number of applications per month.

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OTHER ACTIVITIES IN 2014

Preparation for use of Regulation 536/2014 requires national and European cooperation

New legislation on clinical trials of medicines was adopted in Europe in 2014. Regulation 536/2014 was published on 28 May 2014 and will be applicable as at 28 May 2016 at the earliest.

The new rules imply complex changes of the European regulatory authorities' authorisation and supervision of clinical trials of medicinal products, and we participate in the preparatory work, both nationally and in Europe.

In Denmark, a coordination group has been established with representatives from the Ministry of Health, the secretariat of the National Committee on Health Research Ethics and DHMA. The purpose of this group is to ensure that Denmark has the organisational and jurisdictional set-up required to support the new procedures and systems.

On a European level, DHMA participates in the European Medicines Agency's (EMA) working group on the development of the European database and portal that will support the procedures and improve public access to data. The European database and portal are a condition for applying the rules of the regulation and conditional upon an audit of the system which is approved by the Management Board of EMA.

The European Commission's Ad Hoc group prepares guidelines, and CTFG, in which DHMA also participates, focuses on the operational changes in the member states that are not driven by IT development, such as content of assessment reports, process for the selection of reporting member state and cooperation on the monitoring of safety in trials, as well as on convincing several countries to participate actively in VHP to prepare for the application of the regulation.

Common application portal with the ethics committees, DKMAnet

In the spring of 2014, a new version of DHMA's extranet, DKMAnet, was launched. This portal can be used to submit clinical trial applications to both the ethics committees and DHMA. Three months after launch, we found that there was a need for making a number of improvements that are currently being implemented, and we expect to launch a new version in the autumn of 2015.

In the long term, the plan is to introduce format requirements so that material related to clinical trials on medicinal products is only received via DKMAnet to both the ethics committees and DHMA. We will make an announcement on our website when this function is ready. The project is financed by the Ministry of Health.

New European recommendations related to contraception requirements and Reference Safety Information

In September 2014, the CTFG prepared recommendations related to contraception in clinical trials. Likewise, questions and answers regarding the Reference Safety Information were prepared to serve as a basis for an expectedness assessment of an adverse reaction.
Link to news item (in Danish)

Results in EudraCT

The EudraCT database was expanded in July 2014, so that trial results can be entered and it is no longer a requirement to submit a summary of the report of trial results to DHMA. Link to news item (in Danish)

Notes

This report is primarily based on data from EudraCT, the common European database, which was established with the implementation of Directive 2001/20/EC in 2004. Data were extracted in February 2015 and represent a snapshot of the data and data quality of EudraCT.

The annual report presents data on all trials applied for to DHMA by way of a full application in 2014 and therefore comprises trials assessed in 2015. The report is not corrected for the small number of trials that were withdrawn or rejected in 2014.

The annual report does not reflect the overall medicines development activity in Denmark as many trials are conducted over several years.

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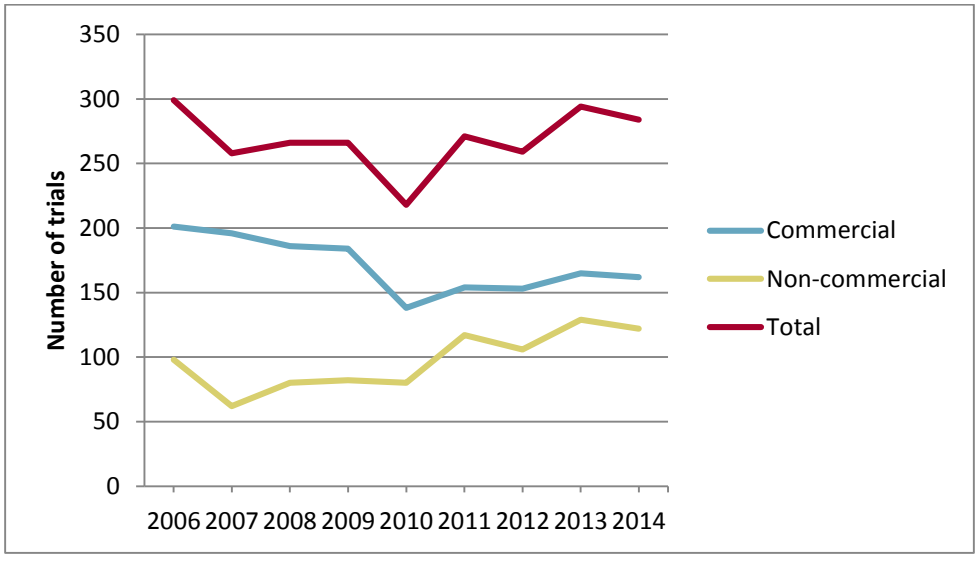
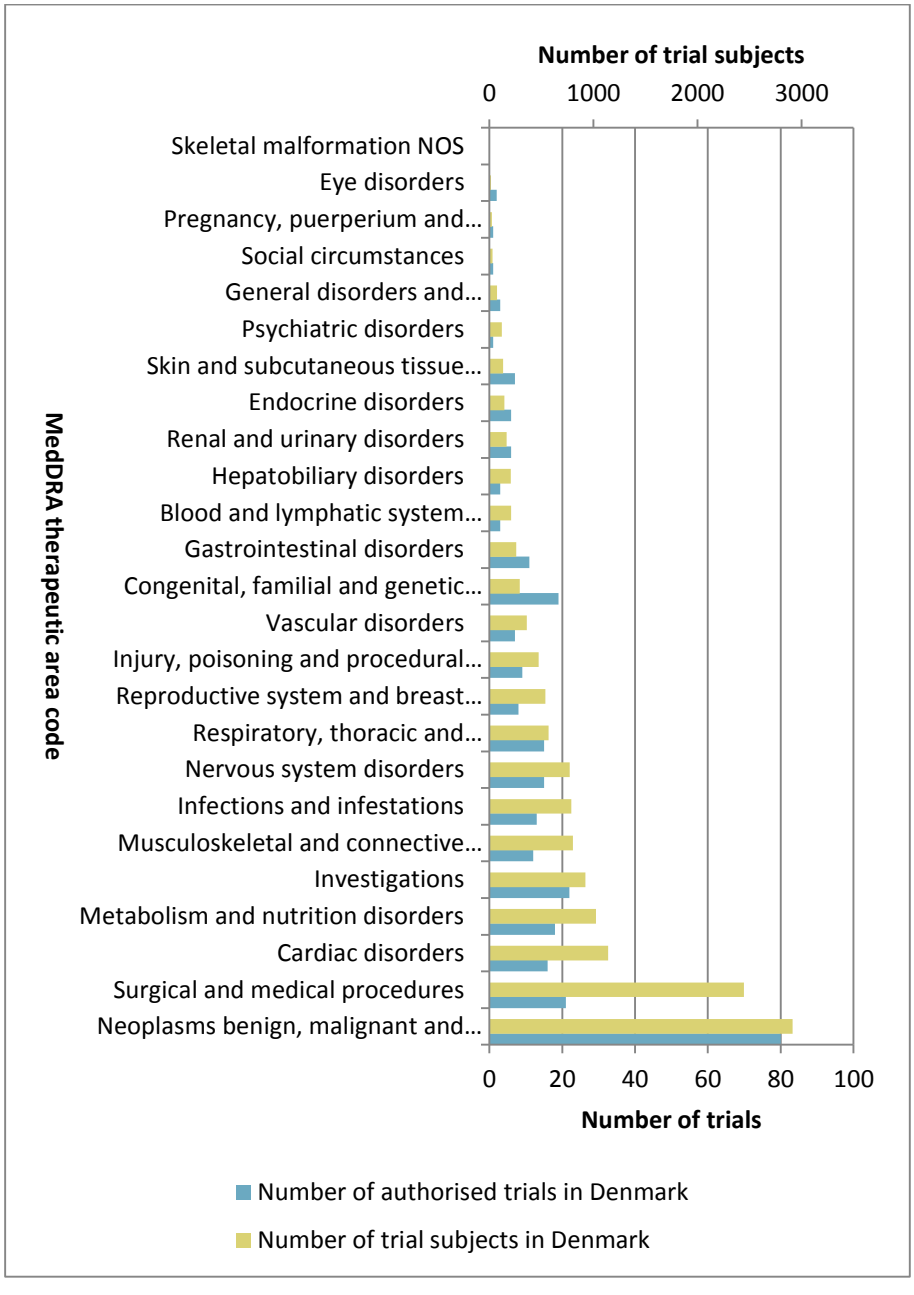
APPENDICES

Appendix 1: Development in the number of clinical trials in Denmark by type of sponsor from 2006 to 2014.



Appendix 2: Distribution of the number of trials and trial subjects on therapeutic area[3]



[3] Trials conducted in several therapeutic areas are included several times. Consequently, the total number of trial subjects and trials in this figure are higher than the numbers reported in the other sections of the report.