Annual report 2011

Clinical trials of medicines in humans

Highlights

Below is a summary of some of the topics covered by the Danish Health and Medicines Authority's annual report on clinical trials of medicines in 2011.

The number of clinical trial applications is back at the 2007 to 2009 level

After having declined by 16 % in 2010, the number of clinical trial applications is back at the same level as in 2009. In 2011, the number of clinical trial applications increased by 45, corresponding to 20 %, and was primarily driven by clinical trial applications sponsored by researchers. The number of clinical trial applications from companies is still considerably lower than the level before 2010.

The number of subjects to participate in trials sponsored by researchers is significantly higher than the number of subjects to participate in trials sponsored by companies

It is estimated that 20,720 Danish trial subjects will participate in the 271 trials that were applied for in 2011. It is estimated that 7,214 of the trial subjects will participate in trials sponsored by companies, whereas 13,506 will participate in trials sponsored by researchers. The average number of subjects per trial is 76. The report breaks down the trial subjects on number of trials and therapeutic areas.

Two thirds of the trials conducted in Denmark are also conducted in other European countries

170 of the 271 trials planned to take place in Denmark will be conducted in several other European countries. Whereas 94 % of the commercial studies are multinational studies, this is only the case for 21 % of the trials sponsored by researchers.

The annual report presents several data on trials notified in 2011 and provides information on some of the national and European activities pursued by the Danish Health and Medicines Authority.

Annual report:

Number of clinical trial applications in 2011 once again reached some 270 trials

Year	Number of clinical trials notified to the Danish Health and Medicines Authority		
	Sponsor, researcher	Sponsor, company	Total
2005	89	215	304
2006	107	229	336
2007	63	207	270
2008	81	194	275
2009	85	183	268
2010	84	142	226
2011	117	154	271

Table 1: Number of clinical trial applications submitted through 2005-2011 by type of sponsor.

In 2011, the Danish Health and Medicines Authority received 271 applications for authorisation of clinical trials of medicines in humans, which is an increase of 45 trials (20 %), on 2010. In 2010, the number of clinical trial applications had fallen by 16 %, and the increase in 2011 has thus brought us back to the level before 2010.

154 of the trials were applied for by commercial sponsors, which is a little more than in 2010. Generally, the company-initiated research activity has been on a downward slope over the past seven years, and the number of applications in 2011 is 33 % lower than it was in 2007, which was a peak year for clinical trial applications submitted by companies.

An increasing number of trials initiated by researchers are notified to us. In 2011, 117 clinical trials were submitted to us, which means that 43 % of the notified trials were initiated by researchers. The number of applications has increased by 33 since 2010.

In Appendix 1, please find a graphical presentation of the development in the number of clinical trial applications from 2006-2011.

Table 2 shows the therapeutic areas within which the most clinical trials are applied for, and in Appendix 2 you can see the distribution of clinical trial applications on therapeutic areas (blue bars).

MedDRA[1] therapeutic area code	Number of clinical trials
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	63
Nervous system disorders	24
Metabolism and nutrition disorders	19
Gastrointestinal disorders	19
Congenital, familial and genetic disorders	17

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

[1] Medical Dictionary of Regulatory Activities

Significantly more trial subjects participate in trials sponsored by researchers than in trials sponsored by companies

It is estimated that 20,720 Danish trial subjects will participate in the 271 trials that were applied for in 2011. It is estimated that 7,214 of the trial subjects will participate in trials sponsored by companies, whereas 13,506 will participate in trials sponsored by researchers.

It appears from Appendix 1 that, since 2009, the number of subjects in trials sponsored by researchers has surpassed the number of subjects in trials sponsored by companies.

The average number of subjects per trial is 76. As illustrated in Figure 1, the number of trial subjects varies considerably – the lowest number of subjects is one, the highest is 1900.

54 clinical trials (20 %) of the trials planned in Denmark have 10 or fewer trial subjects. In six trials, the number of Danish trial subjects exceeds 500, representing almost one third of all trial subjects in Denmark. Four of these six trials were initiated by researchers.

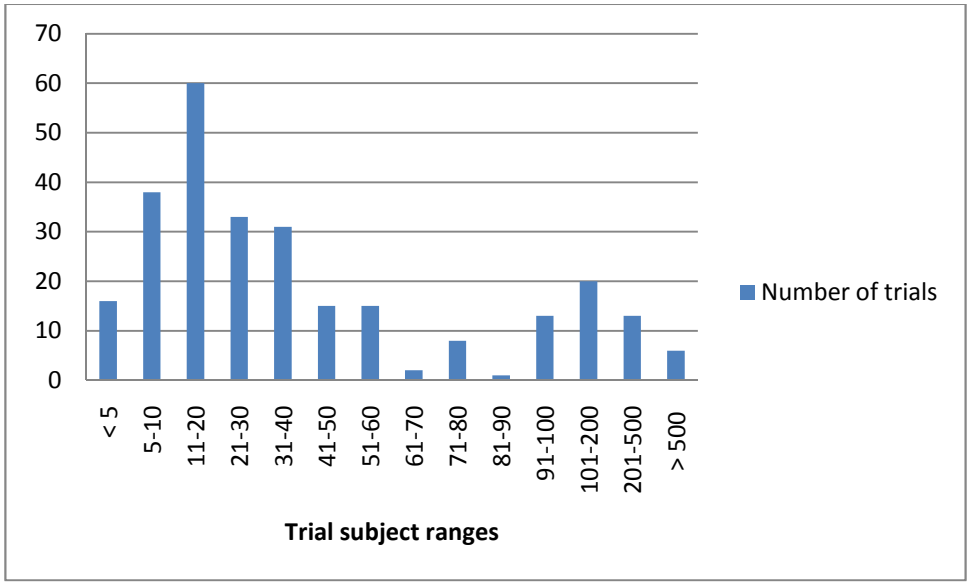


Figure 1: Bar chart of the number of trials in trial subject ranges.

The low number of subjects per trial is presumed to be a result of the fact that many trials are conducted for diseases of low prevalence and because of the evolution towards more targeted treatment in which trial subjects are selected based on a multitude of criteria.

The therapeutic areas with the highest number of clinical trial subjects appear from table 3. In Appendix 2 you can see the distribution of trial subjects on therapeutic areas (red bars).

MedDRA therapeutic area code	Number of trial subjects
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3363
Metabolism and nutrition disorders	2793
Surgical and medical procedures	1843
Cardiac disorders	1738
Vascular disorders	1583

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

Two thirds of the trials planned to take place in Denmark are also conducted in other European countries

It appears from table 4 that 170 (63 %) of the 271 trials concern notified clinical trials of medicinal products expected to take place in several European countries.

Among the 154 commercial trials, 94 % are multinational, but only 6 % of the trials are conducted in Denmark only. 26 (21 %) of the 117 trials sponsored by researchers are multinational. 91 (79 %) trials sponsored by researchers are conducted in Denmark only.

The share of Danish trial subjects participating in multinational trials is 10 % on average, and the number of subjects varies considerably from one to 1900 trial subjects. The proportion of Danish trial subjects ranges from 0.1 % to 88 %.

The large share of multinational trials in Denmark underlines the importance for Danish authorities to participate in and shape the European development of the area and contribute constructively to the harmonisation between the European countries.

	Multinational trials	National trials
All trials	170	101
Sponsor, company	144	10
Sponsor, researcher	26	91

Table 4: Distribution of multinational and national trials by type of sponsor

Distribution of trials by phases:

Figure 2 shows the number of applications according to type of sponsor and clinical trial phase.

There are 20 phase I trials (7 %), 86 phase II trials (31 %), 110 phase III trials (40%) and 60 phase IV trials (22%).

The distribution of trials on trial phases matches previous years, but the share of phase IV trials is increasing, corresponding to the increasing share of trials sponsored by researchers.

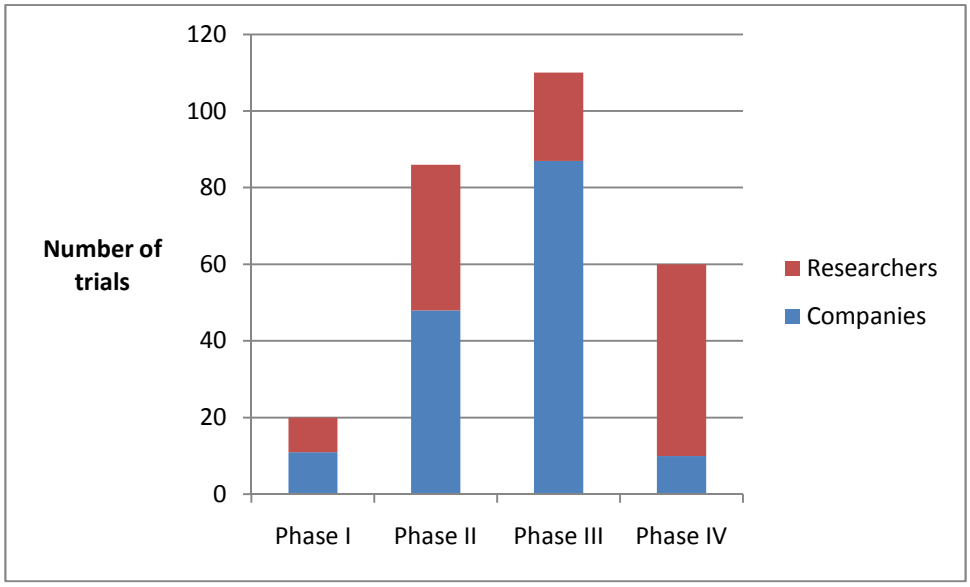


Figure 2: Distribution of clinical trial applications according to trial phase and type of sponsor.

More than half of the clinical trials of medicines are 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.

It is the coordinating investigator's affiliation that determines which ethics committee is to approve the clinical trial, and it appears that 163 (60 %) of the clinical trials of medicines are coordinated from a hospital located in the Capital Region of Denmark. 49 (18 %) are to be coordinated from the Central Denmark Region, 36 trials (13 %) from the Region of Southern Denmark. 18 (6 %) are to be coordinated from the North Denmark Region, 5 trials (2 %) from Region Zealand.

Furthermore, two thirds (99) of the company-sponsored trials are coordinated from the Capital Region of Denmark. The Central Denmark Region coordinates 24 company-sponsored trials, whereas the Region of Southern Denmark coordinates 18. The North Denmark Region has 12 trials, and Region Zealand coordinates one single company-sponsored trial.

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. Therefore, the figure does not point to trends for the overall clinical research activity with medicines in a specific region.

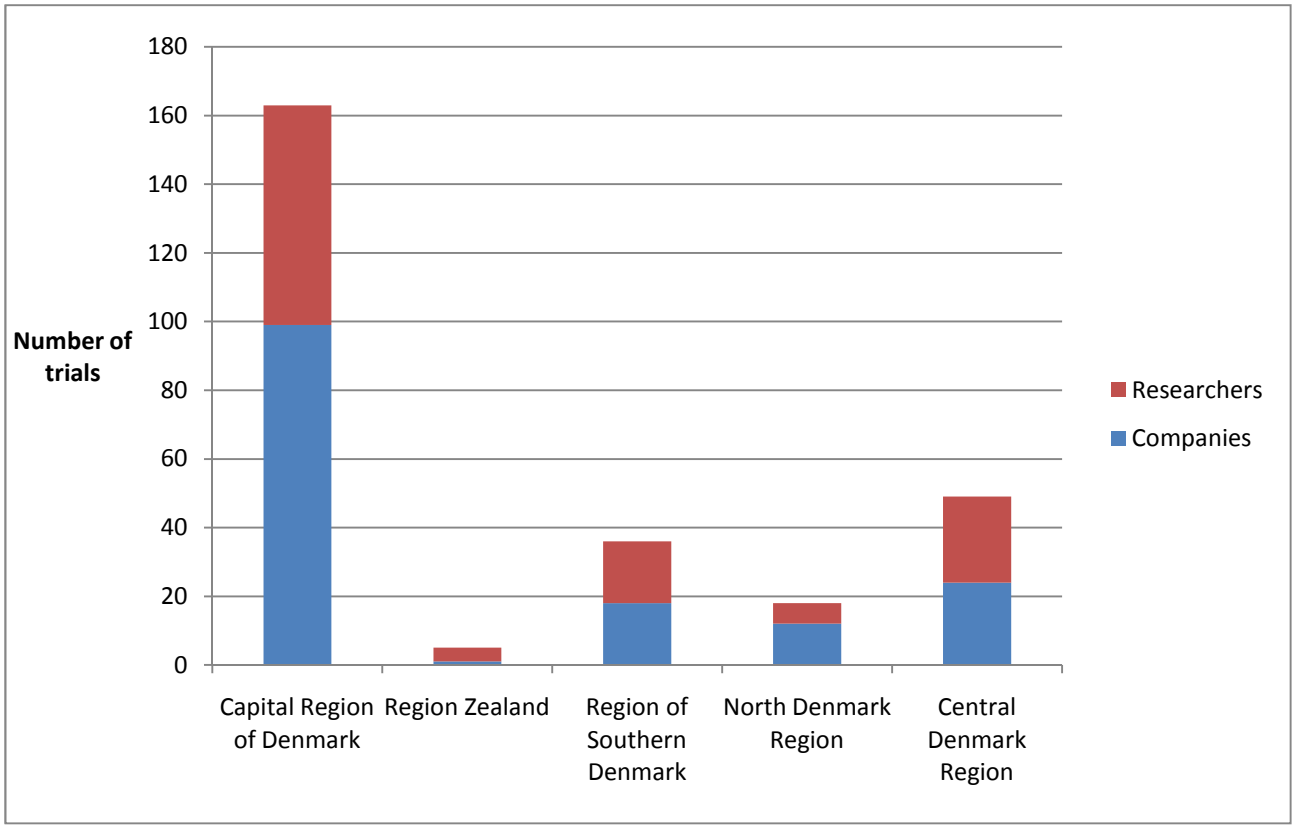


Figure 3: Distribution of clinical trial applications according to type of sponsor and regional affiliation of the ethics committee with which the application has been filed.

The assessment by the Danish Health and Medicines Authority

The work with clinical trials is organised in the Clinical Trials Unit under the Medicines Assessment & Clinical Trials Division. The Clinical Trials Unit has ten full-time and nine 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.

In 2011, the Danish Health and Medicines Authority authorised 267 of the 271 trials applied for. We refused one trial, and three clinical trial applications were withdrawn by the applicant.

Since 2009 it has been possible to obtain a coordinated assessment of an application for a clinical trial that is to take place in several European countries through the Voluntary Harmonisation Procedure (VHP). As can be seen from table 5, the number of cases being reviewed through this procedure is increasing strongly. Denmark participated in 23 cases, which implies that 8 % of the authorisations for the conduct of clinical trials in Denmark have been coordinated with the European authorities in the country where the trial is planned to take place.

The procedure is offered by the European working group CTFG, Clinical Trials Facilitation Group, which was formed by the Heads of Medicines Agencies i 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. You can find more information about the procedure on our website Voluntary Harmonisation Procedure

	2009	2010	2011
No. of cases in the EU	15	26	84
Number of cases with Danish participation	4	3	23

Table 5: Number of cases reviewed through the Voluntary Harmonized Procedure (VHP)

The maximum time allowed for assessment is 60 calendar days[2] as set out in the executive order on clinical trials of medicinal products in humans. In case the Danish Health and Medicines Authority gives grounds for non-acceptance, the sponsor has the opportunity to amend the application once. In order to ensure that the sponsor has the required time to amend the application, it has been agreed with the pharmaceutical

[2] The deadline is extended by 30 calendar days for the review of applications for trials with medicinal products for gene therapy and somatic cell therapy as well as medicinal products containing genetically modified organisms. For these medicinal products, the deadline of 90 days may be extended by a further 90 days in cases where public boards or the like are consulted. Please note that there is no time limit for the Danish Health and Medicines Authority's decision in applications involving medicines for xenogenic cell therapy.

industry that the sponsor is to receive a reply within 30 days, starting on the day the Danish Health and Medicines Authority has received a duly completed application.

In 2011, 97 % of all applications were replied to within 30 working days. The remaining 3 % were replied to at a delay of maximum 15 days. We publish our assessment times on our website Assessment times 2011.

Since May 2011, the Danish Health and Medicines Authority has accepted the submission of electronic clinical trial applications, and since 21 November 2011 companies have been able to apply online via DKMAnet our access-controlled extranet. The application procedure via DKMAnet is user-friendly with step-by-step application forms designed to remind the applicant of which documents to submit with the application. The design is to reduce the number of invalid (incomplete) applications, which presently account for 30 % of the applications.

Other activities in 2011

We continue our close work with our stakeholders

The clinical research area has many stakeholders, both national and European, and we prioritise interaction highly.

The Danish Health and Medicines Authority meets regularly with: The secretariats of the national and regional ethics committees, the Organization of Danish Medical Societies and the Danish Medical Association, the GCP units, the Danish Association of the Pharmaceutical Industry, the pharmaceutical industry's committee for clinical research and gene therapy committee (Danish Environmental Protection Agency, Danish Working Environment Authority and the Danish Health and Medicines Authority). In addition, a series of general and specific training activities are conducted.

On a European level, the Clinical Trials Unit participates in three European working groups: The EU Commission's Ad Hoc group, the Clinical Trials Facilitation Group (CTFG) formed by the Heads of Medicines Agencies as well as EudraCT Telematic Implementation Group under the European Medicines Agency, EMA.

Clarification of the possibility for a common application portal with the ethics committees

Several parties request a simpler application procedure for clinical trials of medicines in Denmark to make it less time-consuming and thus more attractive for researchers and companies to initiate clinical research in Denmark. A project has therefore been initiated that will look into the possibilities of establishing a common application portal, so that applications destined for the Danish Health and Medicines Authority and the ethics committee system can be submitted in one place only. In 2011, the Danish Health and Medicines Authority has contributed with estimates on the scope of such a project.

Risk-adapted assessment now a possibility

During 2011, we assessed the possibility of introducing risk-adapted assessment of clinical trials and offering shorter assessment time for certain types of trials. For a one-year trial period starting in April 2012, we will be offering a 14-day assessment time for trials conducted with medicinal products marketed in an EU or EEA country, provided the medicinal products are tested under the licensed indication and the risk involved for the trial subject is not higher than the risk of standard treatment. More information is available on our website: Risk-adapted assessment.

Data in EudraCT is now publicly available and the data value is increased

The public has been given access to data in the common European database, EudraCT, via www.clinicaltrialsregister.eu. EudraCT contains data about all clinical trials authorised in Europe after the entry into force of Directive 2001/20/EC in 2004, and it has so far been used for the exchange of

information between the authorities. More information is available on our website: Public access to EudraCT.

EudraCT has also been acknowledged as a so-called "primary registry" for WHO's database of clinical trials like the US ClinicalTrials.gov. When an application for authorisation of a clinical trial is filed with the authorities, it is therefore sufficient to publish a study only once. More information is available on our website: Sufficient to publish study in EudraCT.

The European Medicines Agency (EMA) which is responsible for running EudraCT has changed the IT architecture, and it is now possible to target database searches through a Data Warehouse. This makes it easier to use data, for example in an annual report such as this one.

Comments on European development of clinical trials legislation and guidelines.

The European Directive has been criticised by several stakeholders, and the European Commission is presently working on a revision based on two public consultations. The revision is expected to be published in the second half of 2012. For further information please visit this page: Clinical trials - Major developments.

The Commission has also published guidelines to ensure greater harmonisation until the legislative revisions have been implemented.

Among the revised guidelines are the European CT1 guideline (guideline on application, amendments and end of trial). Consequently, we have updated our guideline with the substantial amendments requiring authorisation. For further information, please see this overview: Amendments to clinical trial application (CTA).

Electronic reporting of SUSARs from other EU countries now a possibility

With the possibility of electronic reporting of serious and unexpected adverse reactions (SUSARs), the Danish Health and Medicines Authority has facilitated reporting for pharmaceutical companies that already report SUSARs electronically. Previously, SUSARs from other EU countries were to be submitted on paper. Read more about reporting here Reporting of adverse reactions in clinical trials

Improved guidance on the definition of a clinical trial of medicinal products

In response to uncertainty in the area, we have updated chapter 1 of our Guideline for applications for authorisation of clinical trials of medicinal products in humans with information about whether or not a trial is classified as a clinical trial of medicinal products.

We have also published a guide that can help researchers find out quickly whether a trial is a clinical trial of medicinal products or whether it is possibly a non-interventional study: Guide to assessing if a trial falls under the definition of a clinical trial

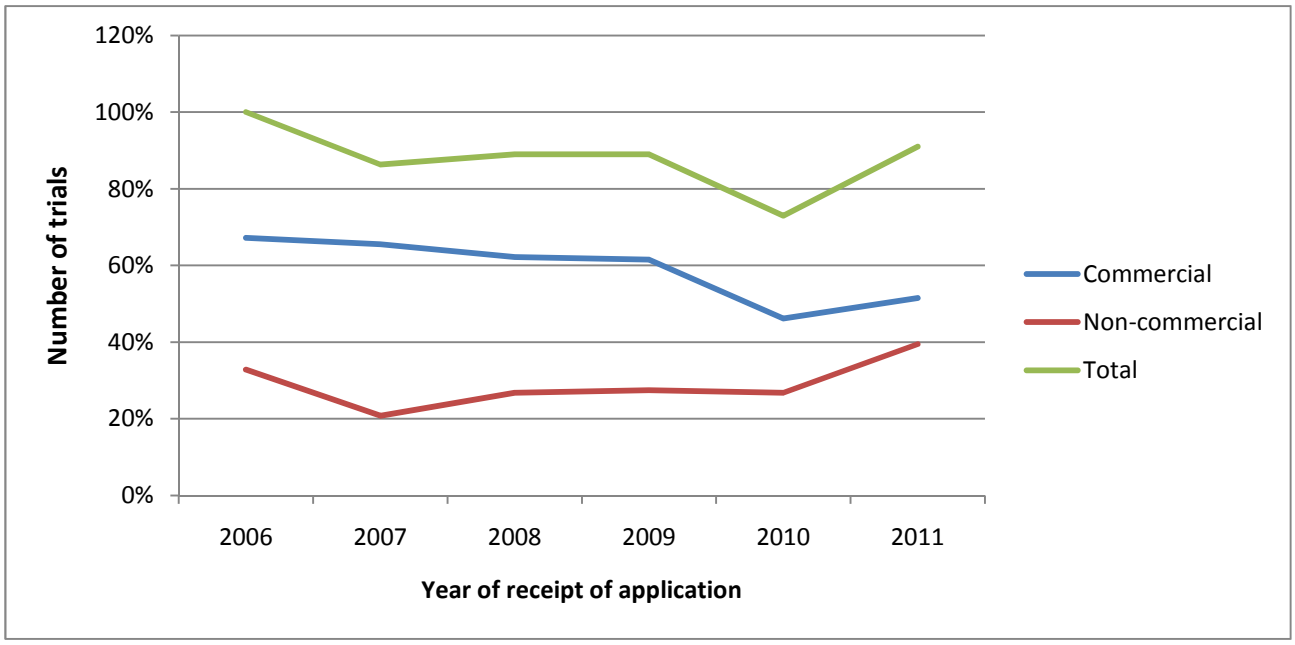
Notes

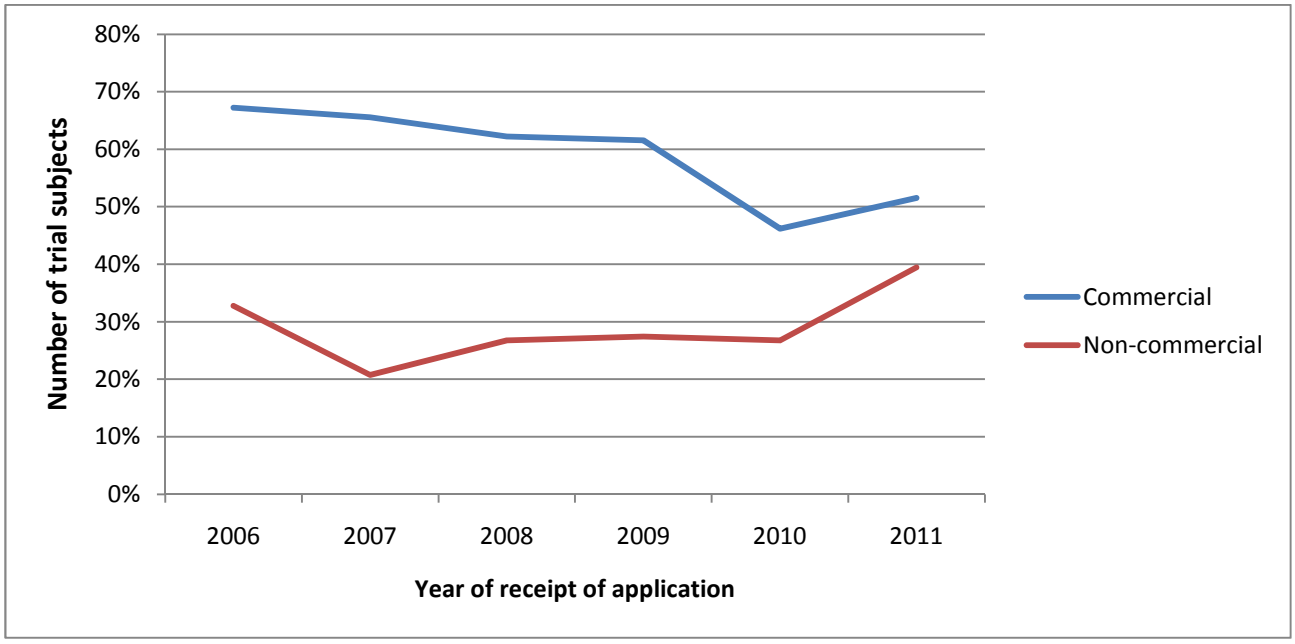
This report is primarily based on data from EudraCT, the common European database, which was established with the implementation of Directive 2001/20/EC in 2004. Data was extracted in April 2012 and represent a snapshot of the data and data quality of EudraCT. It is therefore likely that newer searches would return a somewhat different result.

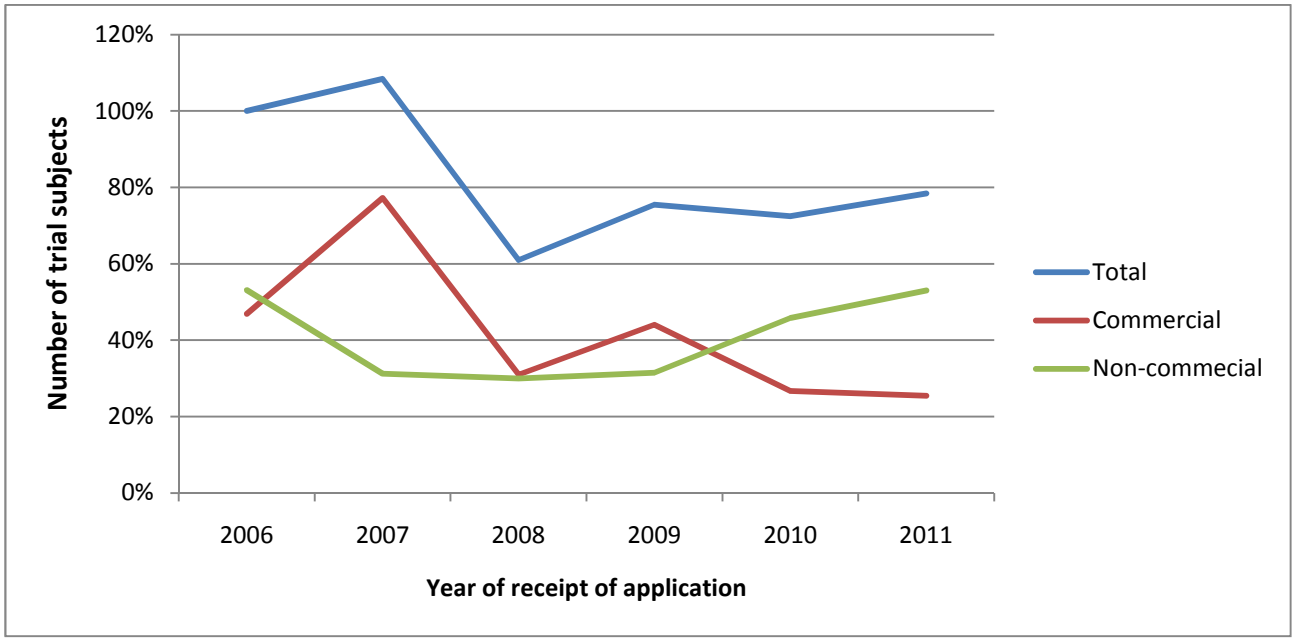
The annual report concerns trials notified in 2011 and does not reflect the overall medicines development research activity in Denmark as many trials are conducted over several years.

On 1 March 2012, the Danish Medicines Agency merged with the Danish National Board of Health under the continuing name Danish Health and Medicines Authority. The described data and activities were thus performed by the former Danish Medicines Agency. We have used the designation Danish Health and Medicines Authority throughout the annual report.

Appendix 1: Relative development in the number of clinical trials in Denmark and number of trial subjects, distributed according to type of sponsor in the period 2006 to 2011.






120%
100%
80%
60%
40%
20%
0%
Number of trial subjects
2006
2007
2008
2009
2010
2011
Year of receipt of application
Total
Commercial
Non-commecial

Appendix 2: Distribution of the number of trials and number of trial subjects on therapeutic area.