Sundhedsstyrelsen
Danish Health and Medicines Authority

Annual report 2012

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 2012.

The number of clinical trial applications is at the same level as in 2011

In 2012, the Danish Health and Medicines Authority received 259 applications for clinical trials, 12 trials down compared to 2011. The number of trials sponsored by companies appears to have stabilised around 150 trials per year.

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 19,150 Danish trial subjects will participate in the 259 trials that were applied for in 2012. It is estimated that 8,605 trial subjects will participate in the 153 trials sponsored by companies, whereas 10,535 will participate in the 106 trials sponsored by researchers. The average number of subjects per trial is 74. 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

160 of the 259 trials planned to take place in Denmark will be conducted in several other European countries. Whereas 94% of the commercial trials are multinational, this is only the case for 15% of the trials sponsored by researchers. The number of multinational trials sponsored by researchers has fallen by 40%.

Assessment times are being met and an increasing number of trials are coordinated with other European authorities

The Danish Health and Medicines Authority has met 98% of the fixed assessment times, and 10% have been reviewed through the common European Voluntary Harmonisation Procedure (VHP). From April 2012, the Danish Health and Medicines Authority has offered shorter assessment times for applications suitable for risk-adapted assessment. The use of this offer has been limited, but it is expected to grow in line with increasing awareness of the offer.

The annual report presents several data on trials notified in 2012. You can also read about the application portal shared with the ethics committees that we will launch in the autumn of 2013, introducing format requirements for clinical trial applications as well as the European Commission's proposal for a clinical trials regulation released in July 2012.

Annual report:
The number of clinical trial applications in 2012 is at the same level as in 2011

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
2012	106	153	259

Table 1: Number of clinical trial applications submitted through 2005-2012 by type of sponsor.

In 2012, the Danish Health and Medicines Authority received 259 applications for authorisation of clinical trials of medicines in humans, which is a fall of 12 trials or 4% on 2011.

153 of the trials were applied for by commercial sponsors, which is on level with 2011. Generally, the company-initiated research activity has been on a downward slope over the past years, but appears to be stabilising around 150 trials per year.

In 2012, the number of trials initiated by researchers declined by 11, corresponding to 9%. In 2012, 106 clinical trials were submitted to us, which means that 41% of the notified trials were initiated by researchers.

In Appendix 1, please find a graphical presentation of the development in the number of clinical trial applications from 2006-2012.

The therapeutic areas with the highest number of clinical trial applications appear from table 2. We still receive most clinical trial applications within the cancer field. The number of clinical trials within metabolism and nutrition disorders has almost doubled from 19 in 2011 to 34 in 2012.

In Appendix 2 you can see the distribution of all clinical trial applications by therapeutic area (blue bars).

MedDRA[1] therapeutic area code	Number of clinical trials
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	60
Metabolism and nutrition disorders	34
Musculoskeletal and connective tissue disorders	24
Infections and infestations	16
Surgical and medical procedures	15

Table 2: Top 5 therapeutic areas measured by number of clinical trial applications in 2012.

[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 19,150 Danish trial subjects will participate in the 259 trials that were applied for in 2012. It is estimated that 8,615 trial subjects will participate in trials sponsored by companies, whereas 10,535 will participate in trials sponsored by researchers.

The average number of subjects per trial is 74. As illustrated in Figure 1, the number of trial subjects varies considerably – the lowest number of subjects is one, the highest is 2,246.

32 clinical trials (12%) of the trials planned in Denmark have ten or fewer trial subjects. Compared to 2011, the number of trials with less than ten trial subjects has declined by 22. In four trials, the number of Danish trial subjects exceeds 500, representing 22% of all trial subjects in Denmark.

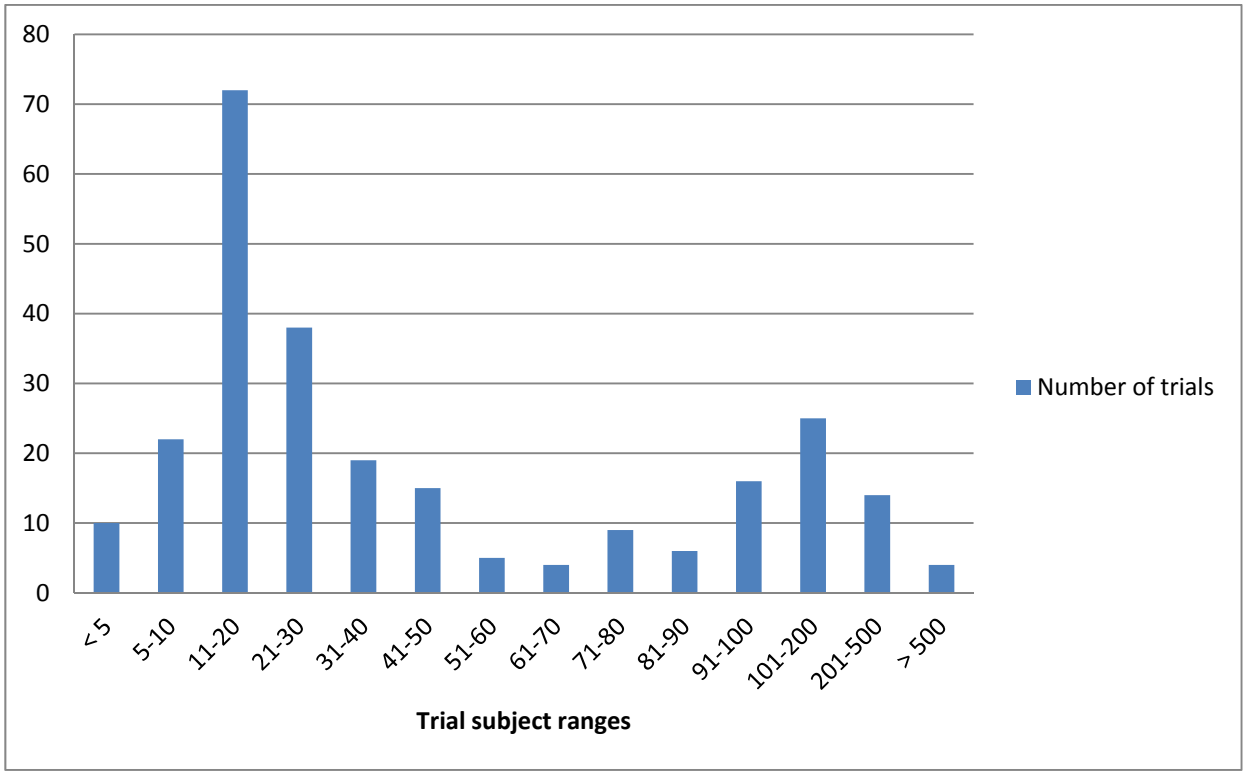


Figure 1: Bar chart of the number of trials in trial subject ranges.

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
Metabolism and nutrition disorders	4,284
Musculoskeletal and connective tissue disorders	3,036
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2,035
Cardiac disorders	1,641
Nervous system disorders	1,496

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 160 (62%) of the 259 trials concern notified clinical trials of medicinal products expected to take place in several European countries.

Among the 153 commercial trials, 144 trials (94%) are multinational, but only 9 trials (6%) are conducted in Denmark only.

16 (15%) of the 106 trials sponsored by researchers are multinational. 90 (85%) trials sponsored by researchers are conducted in Denmark only. The number of multinational trials sponsored by researchers has fallen by 39%, which is significant.

The share of Danish trial subjects participating in multinational trials is 9% on average, and the number of subjects varies considerably from one to 752 trial subjects. The proportion of Danish trial subjects ranges from 0.48% to 78%.

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	
	2011	2012	2011	2012
All trials	170	160	101	99
Sponsor, company	144	144	10	9
Sponsor, researcher	26	16	91	90

Table 4: Distribution of multinational and national trials by type of sponsor in 2011 and 2012.

Distribution of trials by phases:

Figure 2 shows the number of applications according to type of sponsor and clinical trial phase in 2011 and 2012.

There are 26 phase I trials (10%), 78 phase II trials (29%), 111 phase III trials (41%) and 54 phase IV trials (20%).

Compared to 2011, the number of phase IV trials has dropped (6), which is in line with expectations as the share of trials sponsored by researchers declined in 2012. The share of phase I trials has increased by an equivalent number.

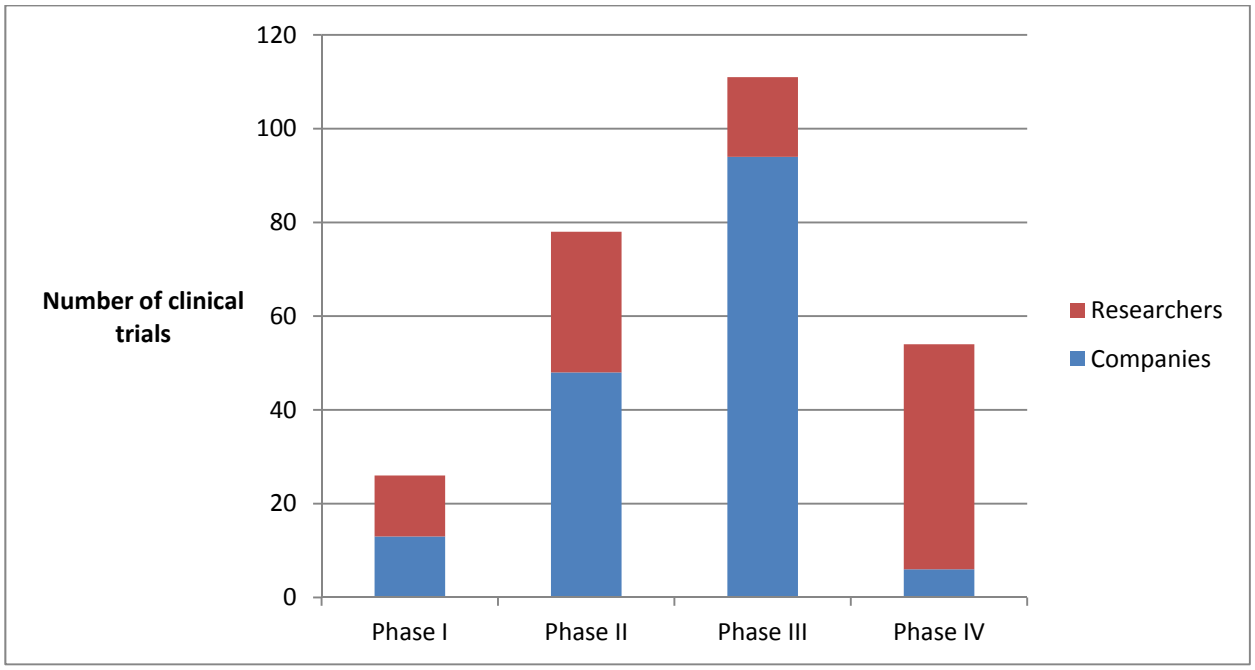


Figure 2: Distribution of clinical trial applications according to trial phase and type of sponsor.

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. The regional distribution of clinical trial applications is broadly in line with 2011.

The coordinating investigator's affiliation determines which ethics committee is to approve the clinical trial, and it appears that 146 (56%) of the clinical trials of medicines are coordinated from a hospital located in the Capital Region of Denmark. 56 (22%) are to be coordinated from the Central Denmark Region, 40 trials (15%) from the Region of Southern Denmark. 9 (3.5%) are to be coordinated from the North Denmark Region, 8 trials (3%) from Region Zealand.

Furthermore, 60% (90) of the company-sponsored trials are coordinated from the Capital Region of Denmark. The Central Denmark Region coordinates 30 company-sponsored trials, whereas the Region of Southern Denmark coordinates 23. The North Denmark Region has 6 company-sponsored trials, and Region Zealand coordinates 4 company-sponsored trials.

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.

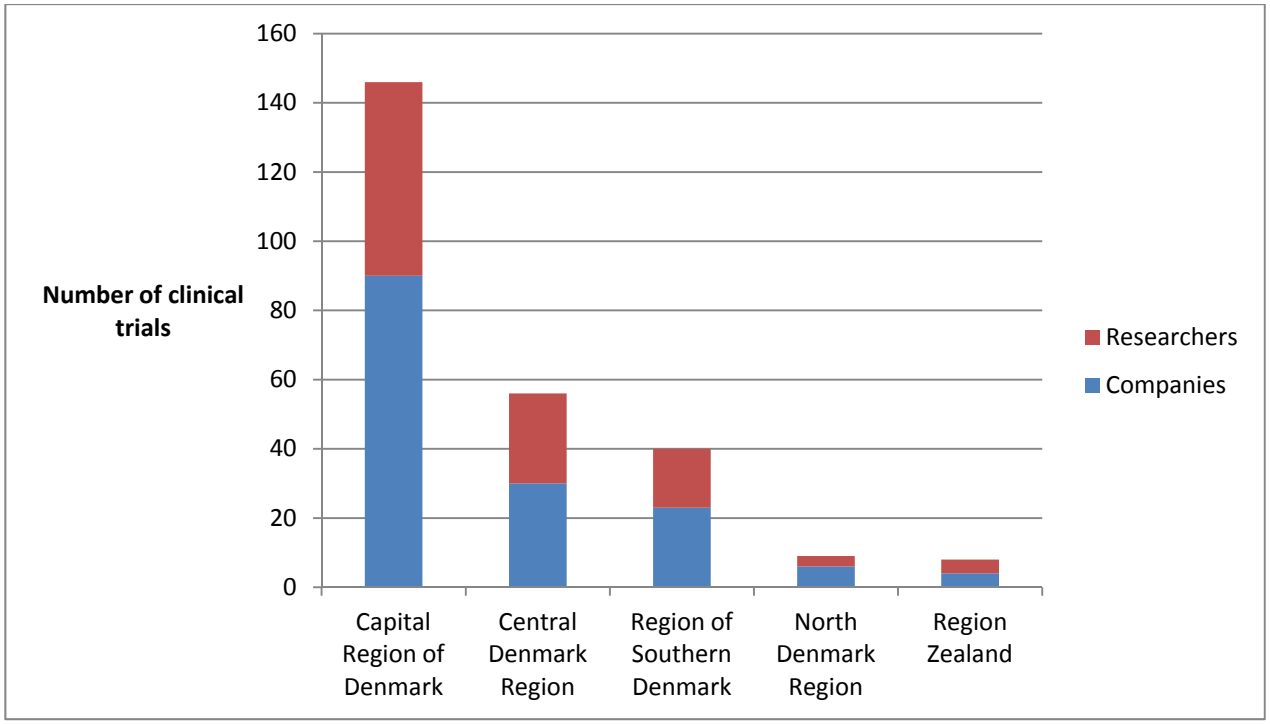


Figure 3: Distribution of clinical trial applications according to type of sponsor and regional affiliation of the ethics committee with which the application has been filed.

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 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.

In 2012, the Danish Health and Medicines Authority authorised 254 of the 259 trials applied for. We refused two trials, 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 24 cases, which implies that 9% of the authorisations for the conduct of clinical trials in Denmark have been coordinated with the other European authorities in the countries where the trials are 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	2012
Number of cases in the EU	15	26	84	124
Number of cases with Danish participation	4	3	23	24

Table 5: Number of cases reviewed through the Voluntary Harmonisation 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 2012, 98% of all applications were replied to within 30 working days. The remaining 2% were replied to at a delay of maximum 15 days. We publish our assessment times on our website Assessment times 2012

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; this should preferably reduce the number of incomplete applications. However, incomplete applications still account for 28% of all applications, and the use of DKMAnet has been disappointing – only 10% of applications are received via DKMAnet.

In connection with the launch of a common portal for clinical trial applications in the autumn of 2013 (see page 13), the Danish Health and Medicines Authority plans to introduce format requirements so that new clinical trial applications and amendments to clinical trials are only received via DKMAnet. We therefore encourage Danish and foreign companies to prepare themselves for the new requirements.

Other activities in 2012

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.

European Commission's proposal for a Clinical Trials Regulation

On 17 July 2012 the European Commission released a proposal for a regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. The main objective of the proposed regulation is to promote the number of clinical trials in the EU, including trials with the same medicinal product in several EU countries.

The proposed regulation aims to harmonise the rules for approval as well as the overall conduct and monitoring of clinical trials throughout the EU.

The proposal sticks to central principles from the applicable Directive 2001/20/EC on good clinical practice in connection with the conduct of clinical trials. As a general principle, a clinical trial can only be conducted provided that the trial subject's rights, safety and welfare are protected and if data from the trial are reliable and robust. Moreover, a number of quality standards for the various trial phases and for the handling of data are also continued.

The proposal also suggests significant changes to the existing system for clinical trials. For example, a new model will be introduced for submission of applications as well as European and national collaboration between member states about authorisation of trials. Clinical trial applications must be submitted to a common EU portal with an accompanying database so that any information about trials in the EU is accessible in one place. Where trials are to be conducted in several countries, the relevant countries' authorities will collaborate on the authorisation, and the national drug regulatory authority and ethics committees will work closely together. The European Commission and the European Medicines Agency provide technical support to the common assessment.

It is also proposed that the member states are obligated to provide for a national indemnification mechanism for compensating damage caused to the subjects in certain clinical trials. Compensation must

be provided taking into account the national liability laws. Other proposed changes include specific provisions on clinical trials in emergency situations, risk-based requirements to the application material, shorter assessment times and simplified rules on safety reporting during the trial period.

The Danish Health and Medicines Authority participates in the negotiations for this proposal in the Council.

Common application portal with the ethics committees in the pipeline

The Danish Health and Medicines Authority acts as project manager for the development of a common application portal for the ethics committee system and the Danish Health and Medicines Authority. The portal will be based on the Danish Health and Medicines Authority's platform DKMAnet and it will be possible to use NemID for submitting applications.

In connection with the launch, format requirements will be introduced so that applications for new trials and trial amendments are only received via DKMAnet, and we therefore encourage Danish and foreign companies to prepare themselves for the new requirements.

The project is financed by the Danish Ministry of Health and Prevention and is expected to be launched in the autumn of 2013; at the same time a solution for promoting patient recruitment on sundhed.dk will also be launched.

Risk-adapted assessment now a possibility

Since April 2012, the Danish Health and Medicines Authority has for a trial period offered shorter assessment times for trials suitable for risk-adapted assessment. A 14-day assessment time is offered for trials which satisfy the following criteria:

- The investigational medicinal products to be tested are authorised in an EU or EEA country.
- The investigational medicinal products are tested in the patient population they are licensed for.
- The investigational medicinal products are tested under the licensed indication, dose and route of administration.
- The risk involved for the trial participants is on the same level as the risk of standard treatment.

More information is available on our website: Risk-adapted assessment

The Danish Health and Medicines Authority has received 12 applications requesting risk-adapted assessment in the period from April 2012 to April 2013, nine of which met the criteria for risk-adapted assessment. This is a very small number, which may be due to the limited awareness of this opportunity. The Danish Health and Medicines Authority encourages applicants to make use of this opportunity.

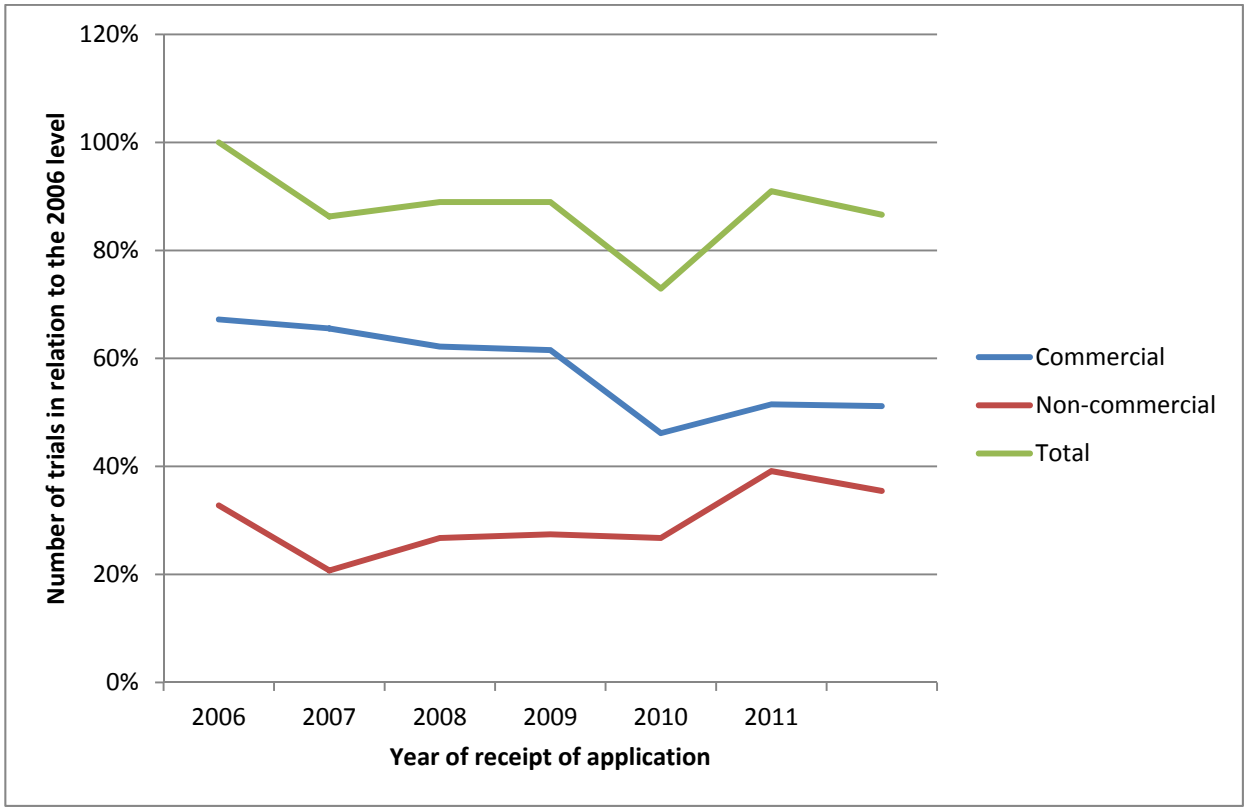
Notes:

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 May 2013 and represents a snapshot of the data and data quality of EudraCT. It is therefore likely that newer searches would return a slightly different result.

The annual report presents data on all trials applied for to the Danish Health and Medicines Authority in 2012 and are not corrected for the five trials that have been withdrawn or refused.

The annual report concerns trials notified in 2012 and does not reflect the overall medicines development research activity in Denmark as many trials are conducted over several years.

Appendix 1: Relative development in the number of clinical trials in Denmark, distributed according to type of sponsor in the period 2006 to 2012.



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