

Project Final Report

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Name, title & organisation of the scientific representative of the project's coordinator:	Prof. Christian Gerloff Universitätsklinikum Hamburg-Eppendorf Tel: +49 40741052770 Fax: +49 40 7410 56721 E-mail: gerloff@uke.uni-hamburg.de
Project website address:	www.wakeup-stroke.eu

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1. Final publishable summary report

The following partners are involved in the project WAKE-UP (www.wakeup-stroke.eu):

No°	Partner	Country
01 UKE	Universitätsklinikum Hamburg-Eppendorf (Coordinator)	Germany
02 AUH	Aarhus University Hospital	Denmark
03 Charité	Charité – Universitätsmedizin Berlin	Germany
04 IDIBGi	Institut d'Investigació Biomèdica de Girona Doctor Joseph Trueta	Spain
05 KUL	Katholieke Universiteit Leuven	Belgium
06 HCL	Hospices Civils de Lyon	France
07 UG	University of Glasgow	United Kingdom
08 SAFE	Stroke Alliance for Europe	Belgium
09 FME	Fraunhofer-Gesellschaft zur Förderung der Angewandten Forschung e.V.	Germany
10 mediri	Medical Imaging Research Institute	Germany
11 ZytoService	ZytoService Deutschland GmbH	Germany
12 GABO:mi	GABO:mi Gesellschaft für Ablauforganisation :milliarium mbH & Co. KG	Germany
13 ORION	ORION Clinical Services Ltd	United Kingdom

1.1 Executive summary

In WAKE-UP, an investigator-initiated, multicentre, randomized, double-blind, placebo-controlled trial was conducted, that was designed to test efficacy and safety of MRI-based intravenous thrombolysis in patients with wake-up stroke. Every year 1.5 million patients suffer a stroke in the EU. Up to 20% of stroke patients wake up with stroke symptoms. Currently these patients are excluded from thrombolysis which is the only approved specific treatment available for acute stroke. However, recently the potential of MRI to identify patients likely to be within a time-window for thrombolysis (≤ 4.5 hours) was demonstrated. The WAKE-UP trial used a specific MRI pattern, i.e. the mismatch between a visible lesion on DWI and a normal FLAIR image, to randomise patients waking up with stroke symptoms to either treatment with Alteplase or placebo. The primary endpoint was favourable outcome at 3 months after stroke.

The WAKE-UP trial was conducted in 70 clinical sites in eight European countries between October 2011 and September 2017. Overall, 1,362 patients were enrolled in the trial, of whom 502 were randomized. By the end of the project, the final follow-up examination of the last patient has been performed and the preparations for the database-lock and final analysis are nearly complete. Results of the clinical trial will be presented at the European Stroke Organisation Conference in May 2018 accompanied by scientific publication in a major journal.

Additional scientific analyses of the data collected in the trial are ongoing including the impact of additional MRI information such as vessel occlusion or perfusion lesion on the treatment effect. During the course of the project, a Japanese companion trial was launched, the Thrombolysis for Acute wake-up and Unclear-onset Strokes With Alteplase at 0.6 mg/kg Trial (THAWS), applying the same concept as established in WAKE-UP to treatment with the reduced Japanese dose of Alteplase in a randomized trial. A joined analysis of WAKE-UP and THAWS will be performed after publication of the primary results of both trials.

Within the WAKE-UP project, a dedicated easy-to-use software for the standardized analysis of acute stroke MRI including lesion segmentation and lesion volume quantification. The trial

was be accompanied by activities increasing the awareness for acute stroke in the public. A dissemination plan was developed ensuring effective dissemination of the projects results within the scientific community as well as within the public.

To summarize, WAKE-UP represents a paradigm-change in acute stroke treatment towards imaging-guided acute treatment instead of treatment relying on information on the time of symptom onset. The results of the trial are expected to provide evidence for effective treatment to a large new group of patients. WAKE-UP may change guidelines of acute stroke management and clinical practice. By this, WAKE-UP will help to reduce the burden of stroke related disability in the EU.

1.2 Summary description of project context and objectives

WAKE-UP is an investigator-initiated, multicentre, randomized, double-blind, placebo-controlled trial designed to test efficacy and safety of MRI-based intravenous thrombolysis in patients with wake-up stroke. Stroke is a devastating disease leading to death and disability in large numbers of patients with massive social and economic impact. Every year 1.5 million patients suffer a stroke in the EU. Intravenous thrombolysis with recombinant tissue plasminogen activator (Alteplase) is the only effective and approved medical treatment for acute ischemic stroke. However, thrombolysis relies on information about the time of symptom onset as it was only demonstrated to be effective and safe within 4.5 hours of symptom onset. It is not approved for stroke patients with unknown time of symptom onset, e.g. patients waking up with stroke symptoms.

In a large number of stroke patients the time point of symptom onset is not known. Up to 20% of acute stroke patients wake up with stroke symptoms. Given the numbers above it can be estimated that wake-up stroke is responsible for approximately 100.000 deaths each year in the EU. Currently, according to approval criteria and guideline recommendations this large group of patients is excluded from thrombolysis, resulting from the fact that the exact time point of symptom onset is unknown in these patients. However, there is compelling evidence that a large proportion of patients waking-up with stroke symptoms might benefit from reperfusion treatment. WAKE-UP will therefore provide novel imaging criteria to identify these patients. In preparatory studies partners of the WAKE-UP consortium have performed pioneering innovative research on the use of modern imaging techniques to improve the understanding of the pathophysiology of acute ischemic stroke and the acute treatment for individual patients based on imaging findings. This preparatory work has lead directly into the design of the WAKE-UP trial. In WAKE-UP, the consortium has incorporated cutting-edge expertise in stroke imaging and extensive expertise in clinical stroke trials into an imaging based large clinical trial of thrombolysis in patients with wake-up stroke. By doing so, WAKE-UP will make the large group of patients with unknown symptom onset potentially eligible for the only effective acute stroke treatment as yet.

MRI as surrogate marker of stroke lesions <4.h hours of age

There is ample evidence for the benefit of intravenous thrombolysis in patients treated within 4.5 hours of stroke onset. This has raised the question of whether the age of ischemic stroke lesions and thus the time window from symptom onset can reliably be estimated by imaging surrogate markers. MRI findings change during the time course of acute cerebral ischemia, and it has been suggested to use the combination of different MRI sequences as a surrogate marker for the age of an acute ischemic lesion. Tissue water changes after ischemic stroke follow a characteristic course: the drop of the cerebral blood flow below a critical threshold leads to a disruption of the energy metabolism, resulting in cytotoxic edema which can be depicted by a reduced apparent diffusion coefficient (ADC) on DWI within minutes of stroke. During the following hours tissue osmolality increases, accompanied by a net increase of water and followed by vasogenic edem. This absolute increase of water content can be detected by T2-weighted MRI. Thus, DWI allows for the detection of acute ischemic lesions

within minutes with a high contrast but does not allow any further conclusions on lesion age during the first hours of stroke, while T2 signal changes might allow further timely allocation of ischemic lesions. Fluid attenuated inversion recovery (FLAIR) imaging with suppression of CSF signal and strong T2 weighting proved superior to T2wI in the detection of ischemic lesions and is usually part of standard acute stroke MRI examinations. The pattern of a visible ischemic lesion on DWI together with normal T2wI or FLAIR is a typical finding in human stroke if imaging is performed within the first hours of stroke.

DWI-FLAIR-mismatch

These observations have led to a new concept, the DWI-FLAIR-mismatch, introduced by the WAKE-UP coordinators (Thomalla et al., 2009) to identify patients likely to benefit from thrombolysis based on the assumed lesion age. In contrast to the previously suggested concept of perfusion-diffusion-mismatch, which labels a mismatch between lesion volumes on two parameter maps, DWI-FLAIR-mismatch refers to the mismatch between visibility of an ischemic lesion in one sequence (DWI), indicating the presence of acute ischemia, while it is not visible in the other sequence (FLAIR), indicating that the ischemic lesion is less than 3-4.5 hours old. Moreover, in contrast to perfusion-diffusion-mismatch, which indicates tissue viability, DWI-FLAIR-mismatch indicates lesion age, which is the essential piece of information missing in wake-up stroke.

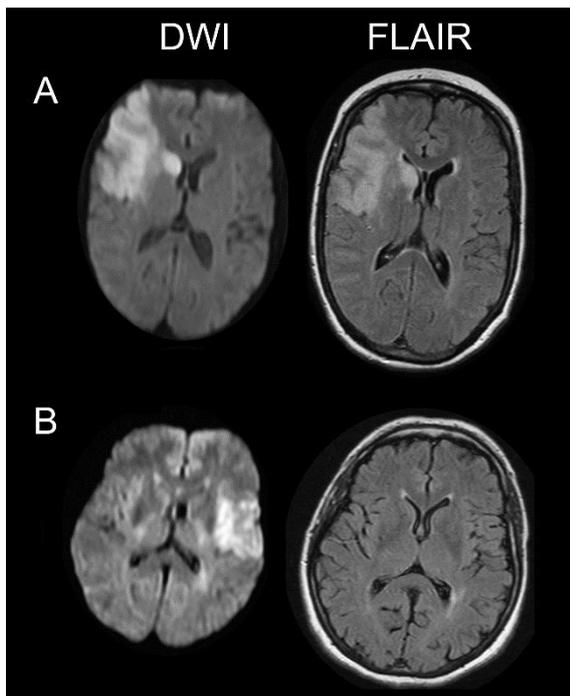


Figure 1: Two different patterns of visibility of acute ischemic lesions on DWI and FLAIR images. Acute ischemic lesions are clearly visible on DWI in both examples. A: Clearly visible acute ischemic lesion on FLAIR 282 min. after symptom onset – “No DWI-FLAIR-mismatch”. B: No acute ischemic lesion visible on FLAIR 125 min. after symptom onset – “DWI-FLAIR-mismatch”.

In a preparatory study, partners of the WAKE-UP consortium were able to show that a mismatch between a visible lesion on DWI and a normal FLAIR (see Figure 1) reliably identifies patients within a time window of ≤ 3 hours with high specificity (0.93) and positive predictive value (0.98) (Thomalla et al., 2009). Following the results from the single centre pilot study, the WAKE-UP coordinators initiated and conducted a large prospective multicentre study which was completed just recently including n=643 patients (PRE-FLAIR: PREDictive value of FLAIR and DWI for the identification of acute ischemic stroke patients ≤ 3 and ≤ 4.5 h of symptom onset – a multicenter study; ClinicalTrials.gov identifier NCT01021319; <http://clinicaltrials.gov/ct2/show/NCT01021319>). This study reproduced the main findings of the previous single centre studies demonstrating 1) a clear time dependency of the visibility of acute ischemic lesions on FLAIR, and 2) high predictive values for the identification of patients with symptom onset < 4.5 hours (Thomalla et al., 2011). Together these studies suggested that the DWI-FLAIR-mismatch allows identifying patients with wake-up stroke with a sufficiently high likelihood of being in a time window in which thrombolysis is

proven effective and safe (≤ 4.5 hours). WAKE-UP used this novel approach of DWI-FLAIR-mismatch to prospectively identify patients for thrombolysis.

The main objectives of WAKE-UP are:

To change clinical practice and to improve the treatment of acute ischemic stroke

WAKE-UP is designed to provide unquestionable evidence for efficacy and safety of MRI based thrombolysis in wake-up stroke patients enabling specific treatment recommendations for acute stroke patients with unknown symptom onset.

To promote a paradigm-change in acute stroke treatment by translating research into clinical practice

Currently, acute stroke treatment critically depends on knowledge of the time point of symptom onset. WAKE-UP will promote a paradigmatic change in patient selection by using novel imaging techniques that hold the promise to identify patients likely to benefit from thrombolysis even if time of symptom onset is unknown.

To enhance the understanding of and optimise multiparametric imaging criteria for patient selection for acute stroke treatment

WAKE-UP will also study the potential impact of other novel imaging strategies such as penumbral imaging and vessel status in response to thrombolysis and by this help in optimizing multiparametric imaging criteria for patient selection for reperfusion treatment.

To provide a tool for the easy integration of modern imaging in acute treatment decisions in daily practice

WAKE-UP will provide a pipeline for the transfer of expert knowledge in acute stroke imaging to a larger number of stroke centres including software tools for image analysis training and computer assisted image processing.

To increase the competitiveness of European stroke research

Bringing together a consortium of renowned stroke researchers with innovative SMEs and enterprises WAKE-UP will set the ground for outstanding power to compete on the highest level in the international competition of stroke research and boost the innovative capacity of European health-related industries.

Rationale for an investigator initiated trial in wake-up stroke

The manufacturer of Alteplase in Europe, Boehringer Ingelheim, has repeatedly denied any interest in funding a trial involving Alteplase in wake-up stroke. Thus, a clinical trial of thrombolysis with Alteplase in wake-up stroke will only be realisable as an investigator initiated trial. In order to avoid any potential conflict of interest or influence by the manufacturer of Alteplase, the study medication in WAKE-UP will be provided by an independent SME. Moreover, patent protection for Alteplase has expired in 2005. Although currently there is no generic available or in preparation, an increased application spectrum might make the development of a biogeneric of Alteplase interesting for the biomedical industry.

Rationale for funding by the EU

Given the large numbers of patients and the joint expertise needed, a trial involving relevant clinical endpoints is only feasible in a large multinational frame as provided by the EU as no single member state has the critical mass to successfully conduct such a trial. WAKE-UP addresses a relevant health problem in the EU and is expected to improve treatment and to change clinical practice. In addition, WAKE-UP follows the European idea of harmonisation and standardisation of medical treatment across the EU. There is still significant regional disparity in morbidity and mortality due to stroke within the EU which – to large parts – results from regional differences in experience with and availability of modern stroke diagnostics and

treatment. WAKE-UP will provide an easy tool for the integration of stroke MRI into clinical practice and thus foster the dissemination of modern stroke diagnostics and facilitate the implementation of best-practice stroke treatment even in centres without long-standing scientific experience in the field. Thus, WAKE-UP will make new and effective treatments available to all EU citizens across knowledge borders and infrastructural boundaries.

1.3 Description of the main S&T results/foregrounds

The core of WAKE-UP activities was the clinical trial designed to test efficacy and safety of MRI-based intravenous thrombolysis in patients waking up with stroke symptoms or patients with unknown symptom onset. Other project activities were either designed to assure the feasibility and success of the clinical trial, to study associated scientific questions, or to the exploitation and dissemination of the trials expected results.

The project was organized in 10 work packages (see Figure 2 for an overview).

WP 01 (Set up framework) set up the framework for the effective and successful execution of the clinical trial. This included the finalisation of the study protocol, setting up the required boards and institutions as well as the clinical and image database and the infrastructure for the supply with the study medication within the trial.

WP 02 (Define imaging standards, training) provided the final definition of imaging inclusion and exclusion criteria, being a crucial part of the trial. A web-based training software was developed, and a standardised comprehensive training and certification process was developed and executed that all trial investigator had to pass prior to enrolling patients in the trial. By this, we were able to assure homogeneous high quality of image judgement in all participating centres.

WP 03 (Clinical trial) comprised the European interventional, treatment, randomised, double-blind, placebo-controlled, parallel assignment, efficacy and safety study, i.e. the WAKE-UP clinical trial. The organisational structure involved a Central Trial Management at UKE in Hamburg, Germany, National Coordination Centers in the participating countries, a clinical research organisation responsible for trial monitoring, effective data management, and trial sites responsible for enrollment of patients. During the course of the trial, 70 sites in eight European countries participated in the clinical trial. Together with WP03, work packages 01, 02, 04, 05, and 06 were directly involved in the execution of the trial and fulfilment of essential tasks related to the clinical trial.

WP 04 (Data and safety monitoring, ethics) comprised the responsibility for data and safety monitoring and ethics. A data safety and monitoring board (DSMB) and an Ethics Advisory Board (EAB) were established and active throughout the project period. WP04 ensured the safety of patients and that the trial was performed according to ICH-GCP guidelines and to international, European and national legislation.

WP 05 (Central image reading) perform central image reading of all images acquired within the clinical trial. Overall, more than 3.700 readings were done. Image review comprised the review of all images as regards the compliance with the inclusion criteria, vessel status readings, and safety readings, i.e. the evaluation of hemorrhagic complications on follow-up images.

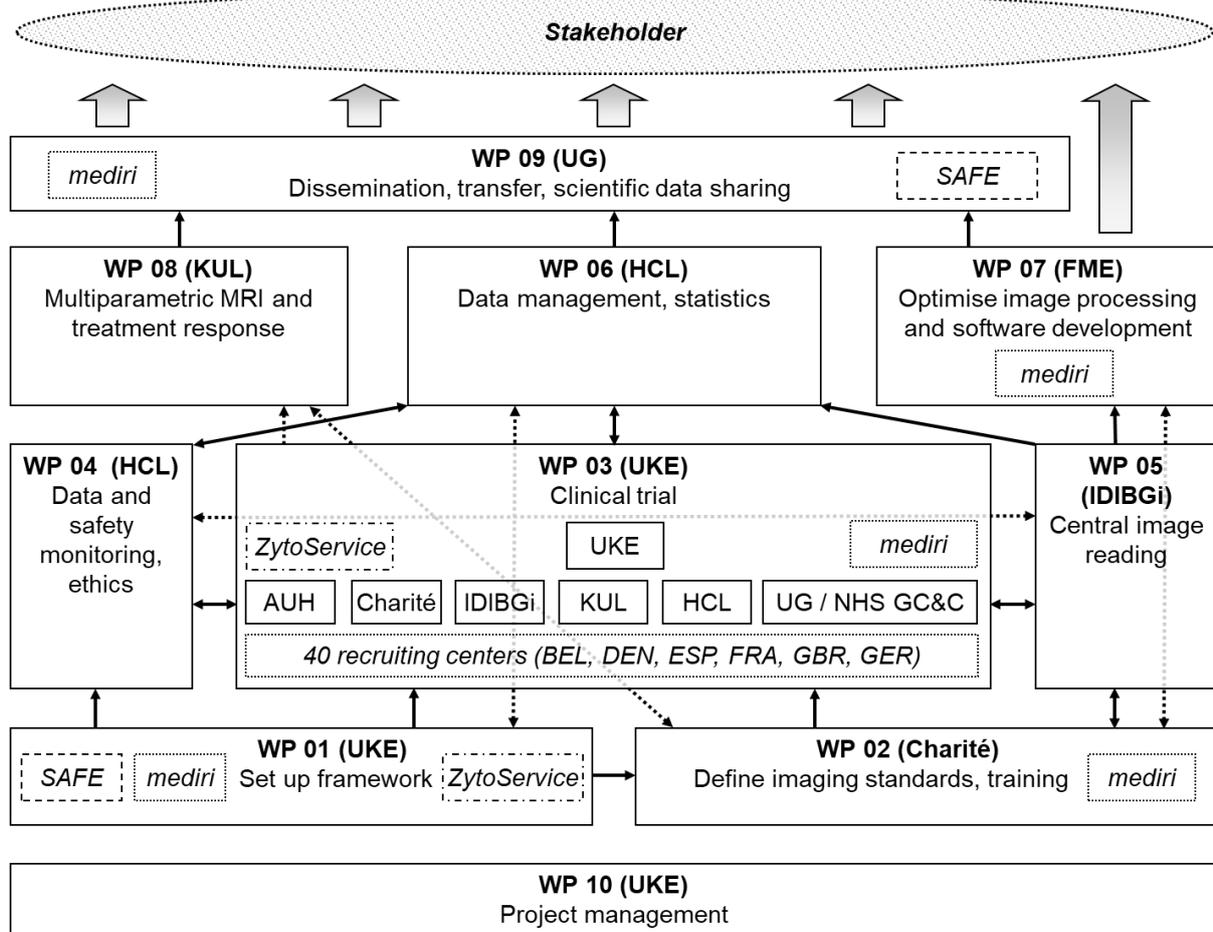


Figure 2: Organisational structure of the WAKE-UP project – work packages and interdependencies between the work packages

WP 06 (Data management, statistics) took over responsibility for data management and statistics. This included data quality checks, regular database exports for analysis, execution of interim analyses as specified in the trial protocol, the development of the final statistical analysis plan, and the final statistical analysis, which is currently ongoing.

WP 07 (Optimise image processing, software development) developed a software tool for standardise image processing and presentation which is now available for scientific use.

WP 08 (Multiparametric MRI and treatment response) has defined the workflow and scientific questions for the analysis of extended MRI studies acquired within the trial including the evaluation of MR profiles previously suggested to identify patients likely to benefit from thrombolysis such as perfusion-diffusion-mismatch and vessel status.

WP 09 (Dissemination, transfer, scientific data sharing) coordinated activities with regards to dissemination of the results of WAKE-UP within the scientific community and the public from the beginning of the project. Moreover, activities fostering the transfer of the results of WAKE-UP into clinical practice were made and scientific collaboration in ongoing international research projects and clinical trials was coordinated.

WP 10 (Project management) covered project management and administration of the project ensuring the proper scientific management of the project, the fulfilment of the contractual duties, and the management of intellectual property issues.

Getting the trial started (WP 01)

During the first year of the project, the framework for the successful start and execution of the clinical trial was established.

- The clinical trial protocol was drafted, reviewed by the external scientific advisory board and the ethics advisory board and finalized (final protocol, version 3.0, 26-Apr-2012).
- WAKE-UP was registered with the EU Clinical Trials Register (EudraCT no. 2011-005906-32) and ClinicalTrials.gov (Clinical-Trials.gov Identifier NCT01525290).
- WAKE-UP was approved by ethic committees in all participating countries.
- The trial also received approval by the Voluntary Harmonized Procedure (VHP) and was approved in the national step by competent authorities all participating countries.

All institutions and boards needed for the steering, conduct, and overview of the trial were constituted:

- trial steering committee (SC)
- ethics advisory board (EAB)
- central image reading board (CIRB)
- data and safety monitoring board (DSMB)
- safety adjudication committee (SAC)

The infrastructure for supply with the study medication was set up. This involved the development and production of placebo not distinguishable from the active drug for the clinical trial which was organized and coordinated by ZytoService. An agreement was made with Boehringer Ingelheim, the manufacturer of the active drug (alteplase). The active drug is bought and relabeled according to the trial specifications. A medication inventory was developed and implemented in the eCRF and a workflow for the continuous supply of trial sites with study medication was defined. See Figure 3 for an illustrated photo of the study medication.



Figure 3: Study medication

An imaging database was set up for uploading of all trial related brain images acquired within the trial. A dedicated workflow was defined for uploading and further processing of images by the Central Image Reading Board (together with WP05). The following software tools were developed to ensure the proper handling and processing of images in WAKE-UP:

- The WAKE-UP Transfer Tool (Transfer Wizard) developed by mediri for image upload to the central image database including de-identifying to ensure privacy and comply with data safety regulations.

- The WAKE-UP Image Reading and Management system provided by mediri giving the central image readers access to images and collecting and storing the information provided from central image reading (together with WP05).
- A DICOM image viewer capable of streaming images to a Web-Browser developed by FME. The viewer has been integrated into the WAKE-UP Image Reading and Management system provided by mediri, and is displayed as part of the imaging eCRF form once a reader selects a case from his worklist
- The WAKE-UP Safety Board Application (SABA) provided by mediri which enables the Safety Adjudication Committee to access all brain images during the process of safety adjudication

Recruiting sites to participate in the clinical trial were identified in each of the participating countries by the national coordinators. Recruiting sites were chosen based on their clinical expertise and track record of successful participation in previous clinical stroke trials. In total, for the start of the trial a network of 40 recruiting sites was identified (see Figure 4).

The infrastructure for management of clinical and imaging data in the clinical trial was established. This included the development of a web-based electronic case record form (eCRF, ClinCase, provided by Quadratek Data Solutions Ltd.) individually tailored to the needs of WAKE-UP. The eCRF includes an interactive web-based randomization tool to enable fast randomization stratified according to age and clinical severity of patients.

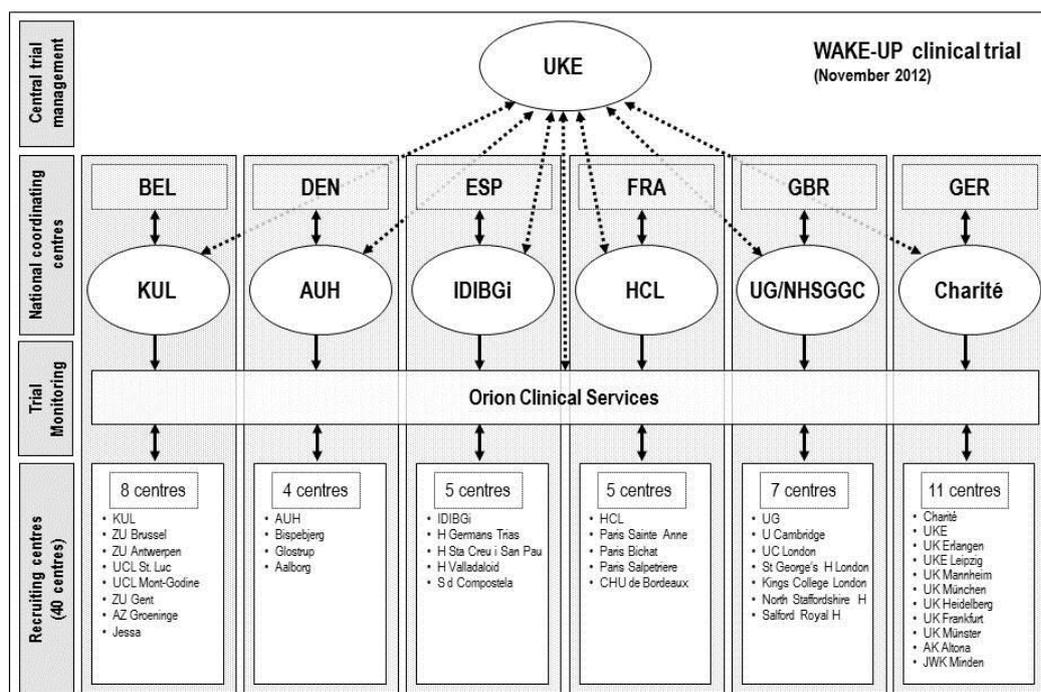
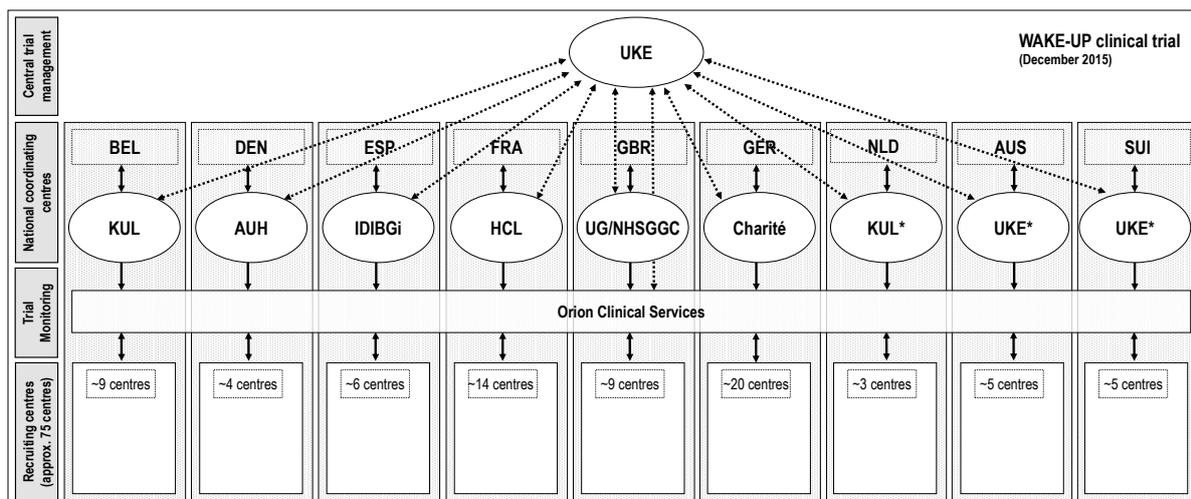


Figure 4: Original organizational structure of the clinical trial

During the course of the trial, a pre-specified contingency plan was deployed in the 3rd reporting period as planned. This comprised an increase of the number of participating study sites. In addition, the trial was extended to two further European countries (Netherlands and Austria) in order to increase enrolment rates. See Figure 5 for the final organisational structure of WAKE-UP.



* Sites in the Netherlands are coordinated by KUL (Belgium); sites in Austria and Switzerland are coordinated by UKE (Germany)

Figure 5: Final organizational structure of the clinical trial

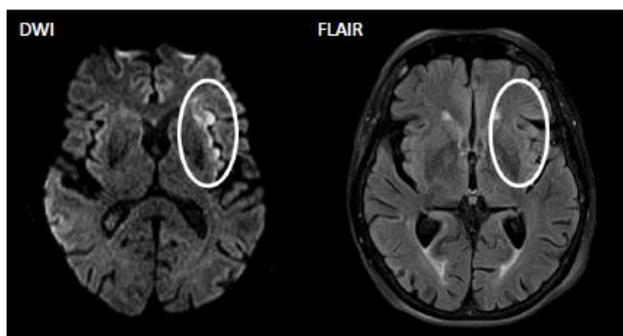
Imaging acquisition and evaluation standards, investigator training and certification (WP 02)

Magnetic resonance imaging (MRI) based criteria were a crucial part of the patients' selection process for the WAKE-UP trial. Although some of the MRI criteria have been used in previous trials and are well established, the trial also introduced a novel criterion, namely the DWI-FLAIR mismatch (the visibility of acute stroke on diffusion-weighted imaging (DWI) combined with its invisibility on fluid-attenuated inversion recovery (FLAIR)). A substantial body of evidence has been able to correlate this sign to the age of the ischemic lesion (and thereby to the time since stroke onset), thus ensuring that patients recruited based on the presence of a DWI-FLAIR mismatch have high odds of benefiting from thrombolytic treatment.

A team of stroke imaging experts defined detailed MRI inclusion and exclusion criteria for the trial. These were made available to all recruiting centers in the form of an illustrated imaging manual as well as an additional booklet. The same team of stroke imaging experts defined standards for MRI image acquisition, which were distributed to all recruiting centers and quality checked once per center prior to the beginning of the trial (see Figure 6).

Main imaging question of the WAKE-UP study:

Is a diffusion restriction (left) already visible in the FLAIR image (right)?

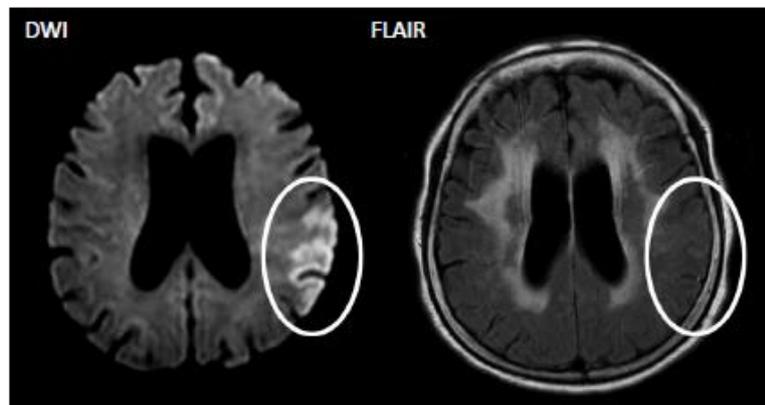


MAIN IMAGING CONCEPT OF THE STUDY

FLAIR positive vs FLAIR negative

The diffusion restriction (left) is not already visible in the FLAIR image (right), making the patient "FLAIR negative"

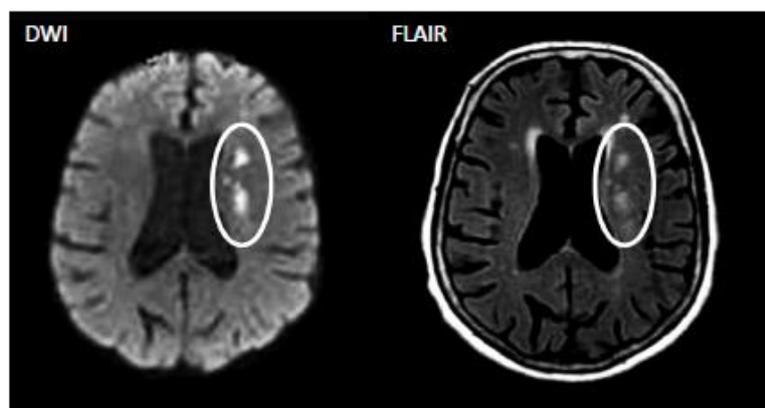
Suitable for randomization in WAKE-UP



FLAIR positive vs FLAIR negative

The diffusion restriction (left) is already visible in the FLAIR image (right), making the patient "FLAIR positive"

Not suitable for randomization in WAKE-UP



4

Figure 6: Comprehensive image troubleshooting handbook (Screenshot pages 3/4 of 81)

Investigators in the individual recruiting centers conducted the enrollment of patients into the trial. From this follows that the same individuals had to acquire good working knowledge of the MRI-based criteria. In order to achieve this, all investigators were required to take part in a centralized procedure of image training which included a final exam. For this purpose we have developed a web-based software tool with a training mode (using real patient images to show all the imaging criteria) and an exam mode (to be entered once the trainee felt confident enough to be able to correctly assess neuroradiological images of a dozen exemplary patients). Test results were evaluated centrally and physicians' eligibility to become investigators depended on the successful completion of the exam.

Overall, 436 investigators have completed the web-based training and certification and thus qualified to apply imaging criteria within the trial. A systematic description and scientific analysis of this investigator training and certification process is currently submitted for scientific publication.

Prior to site activation, quality of MR images used for patient enrollment in the trial at each site was checked. In all 70 active sites MR images complied with protocol and quality requested for the trial.

Central Image Reading (WP 05)

Imaging findings were a crucial part of inclusion and exclusion criteria in WAKE-UP. Thus, the highest quality of acquisition and analysis of MR images as well as image judgement conforming to the inclusion and exclusion criteria defined in the trial protocol were of major importance for the success of the clinical trial. To ensure this, all images acquired within the clinical trial were centrally reviewed by a board of neuroradiologists experienced in stroke imaging.

A central image reading board (CIRB) was established and overall, more than 3,736 readings were performed. In most cases of the readings (88%) there was an agreement between the site and the reading board, and only in a small group of patients (12%) a disagreement was detected (see Figure 7).

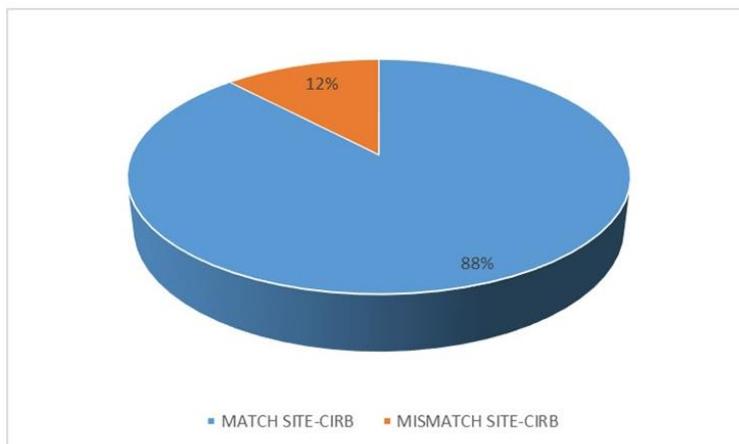


Figure 7: Overview of match and mismatch of Central Image Reading with local judgement

There are two types of mismatch scenarios. In 112 patients (70%), the site decided to exclude a patient, while the CIRB considered that the patient should have been included. In a smaller group of 47 patients (30%), the site decided to include the patient but the CIRB considered that the patient should have been excluded. The main reason of disagreement was a tendency of overestimation the signal intensity on FLAIR. Feedback was sent to the specific sites and junior readers.

Safety image reading comprised the identification and classification of intracerebral haemorrhages representing primary and secondary safety endpoints as well as the judgement of new stroke lesions or malignant swelling. Vessel status readings were made to classify vessel occlusion.

Data and safety monitoring, ethical oversight (WP 04)

The overall aim of the WAKE-UP trial is to improve the treatment of patients with acute ischemic stroke, and specifically of those without a known time of symptoms onset, including 'wake-up' stroke patients, representing up to 20% of all ischemic stroke cases. Intravenous thrombolysis is expected to increase the rate of cerebral reperfusion in patients who were appropriately selected by MRI, and thus increase the odds of a favourable clinical outcome. Conversely, intravenous thrombolysis can cause severe, possibly fatal, intracranial bleeding with neurological deterioration (in ~2% of patients). We took several comprehensive measures in order to ensure the optimal safety of patients throughout all stages of the project.

The safety work package (WP 04) continuously monitored the trial and ensured that the WAKE-UP trial was performed according to ICH-GCP guidelines and to international, European and national legislations with support from an independent Data and Safety Monitoring Board (DSMB). The safety of included patients at the local trial sites was continuously monitored with notification of all serious adverse events (SAE) within 24 hours, and subsequent assessment of their causal relationship to the IMP by the Safety Desk. An evaluation of all safety relevant outcomes was performed by the Safety Adjudication Committee. Ethical oversight of the trial was performed by an independent Ethics Advisory Board.

Two essential committees were formed:

- The Ethics Advisory Board (EAB) oversaw the trial and guaranteed that the trial was performed according to ICH-GCP guidelines and to international, European and national legislations. The EAB could recommend an amendment to the clinical trial protocol or the termination of the trial in case of ethical concerns.
- An independent Data and Safety Monitoring Board (DSMB), whose chair was not involved in the conduct of the trial, performed interim analyses at prespecified time points; the DSMB had the authority to halt the trial in case of any doubt regarding the safety.

The final safety report analyzed a 5-year period from Sep. 23rd 2012 to Sep. 22nd 2017. In this period, 138 reports identified 200 serious adverse events (SAE) that occurred in 111 patients (1 patient can experience several SAE), including 16 fatal cases (3.2% of all randomized patients). The majority of the SAE concerned central nervous system disorders, and were typical of patients admitted for an acute ischemic stroke. Twenty SAE reports (out of 138) were assessed to be related to the investigational medicinal product (IMP: alteplase or placebo). Among the 16 fatal cases, 4 were adjudicated as related to the IMP.

Overall, the Safety Adjudication Committee, EAB and DSMB reported no safety or ethical issue of concern throughout the clinical trial.

Within the project, a specific research focus was the problem of informed consent in acute stroke trials. Any research involving human subjects requires voluntary participation based on informed consent. This also applies to enrolment in clinical trials and usually requires participants to give written informed consent after having received detailed information about potential benefit and risks as well as alternative treatment options, and after having had adequate time for consideration. Trials in acute stroke, however, present several challenges to this approach. Both routine care and clinical trials in acute stroke are carried out under pressure of time. Thus, time available for consideration is very short. In addition, the brain injury commonly compromises language function, awareness of neurological deficits, conscious level, and physical abilities, including vision and writing, relevant to the usual consent process. Since most stroke patients lack capacity to provide consent, alternative approaches are needed. Informed consent was identified as a key factor limiting enrolment in stroke trials, and the bias introduced by systematic exclusion of certain subgroups of stroke patients, e.g. those with aphasia, has been reviewed critically. In WAKE-UP, in line with European and national legislation, we developed a workflow for informed consent comprising surrogate consent by next of kin or independent physicians that allowed us to also enroll incapacitated patients (see Figure 8).

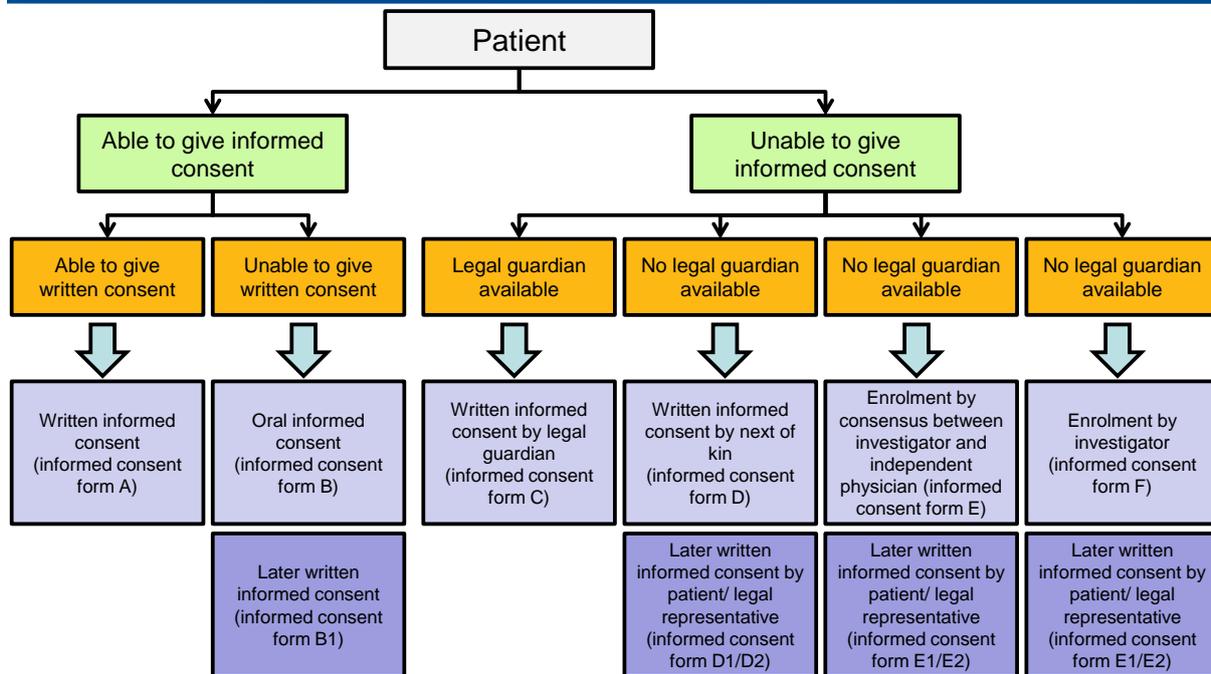


Figure 8: Overview of informed consent in the WAKE-UP trial

In addition, we used the data of the first 1,005 patients enrolled in the trial, to study the heterogeneity of the approach towards consent between the different participating countries as well as the impact of the manner of informed consent on patient characteristics in the trial. The rate of proxy consent differed largely among countries ($p < 0.0001$) ranging from 77.1% in Spain to 1.2% in Denmark (see Figure 9).

Patients recruited by proxy consent were older, had more severe strokes, and higher prevalence of aphasia than those with capacity to give personal consent. Variations in the manner of consent across countries may have an impact on trial results. Results of this analysis were published under open access in a high-ranked neurological journal (Thomalla et al., Effect of informed consent on patient characteristics in a stroke thrombolysis trial. *Neurology*. 2017;89:1400-1407).

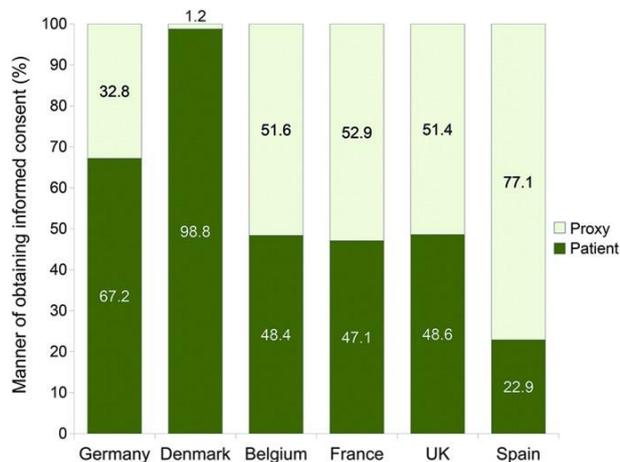


Figure 9: Manner of obtaining informed consent by country (from: Thomalla et al., Effect of informed consent on patient characteristics in a stroke thrombolysis trial. *Neurology*. 2017;89:1400-1407)

Data management and statistical analysis (WP 06)

The clinical trial protocol was reviewed, sample size calculation was completed, a plan for statistical analysis was drafted. The randomisation list was provided and a randomisation dummy run was performed.

During the course of the trial, data quality of all data collected in the clinical trial was continuously checked. Regular database exports for analysis and execution of interim analyses as specified in the trial protocol were performed. Annual analyses of safety data were performed to inform the Developmental Safety Update Report (DSUR) which was submitted to the competent authorities and ethics committees. In addition, three safety interim analyses were performed after randomization of 100, 200 and 300 patients.

The statistical analysis plan was finalized after discussion in the trial steering committee. Final statistical analysis based on all randomized patients (intention to treat principle) is planned to be performed in February 2018.

The clinical trial (WP 03)

WAKE-UP (Efficacy and safety of MRI-based thrombolysis in wake-up stroke: a randomised, double-blind, placebo-controlled trial; Clinicaltrials.gov identifier NCT01525290; EudraCT No.: 2011-005906-32) was an investigator-initiated, randomised, double-blind, placebo-controlled trial designed to test the efficacy and safety of intravenous thrombolysis in patients with unknown time of symptom onset selected by MRI.

The first patient was enrolled on 12 October 2012. Active sites increased continuously, and increasing numbers of patients were enrolled and randomized into the trial (see Figure 10 for an overview).

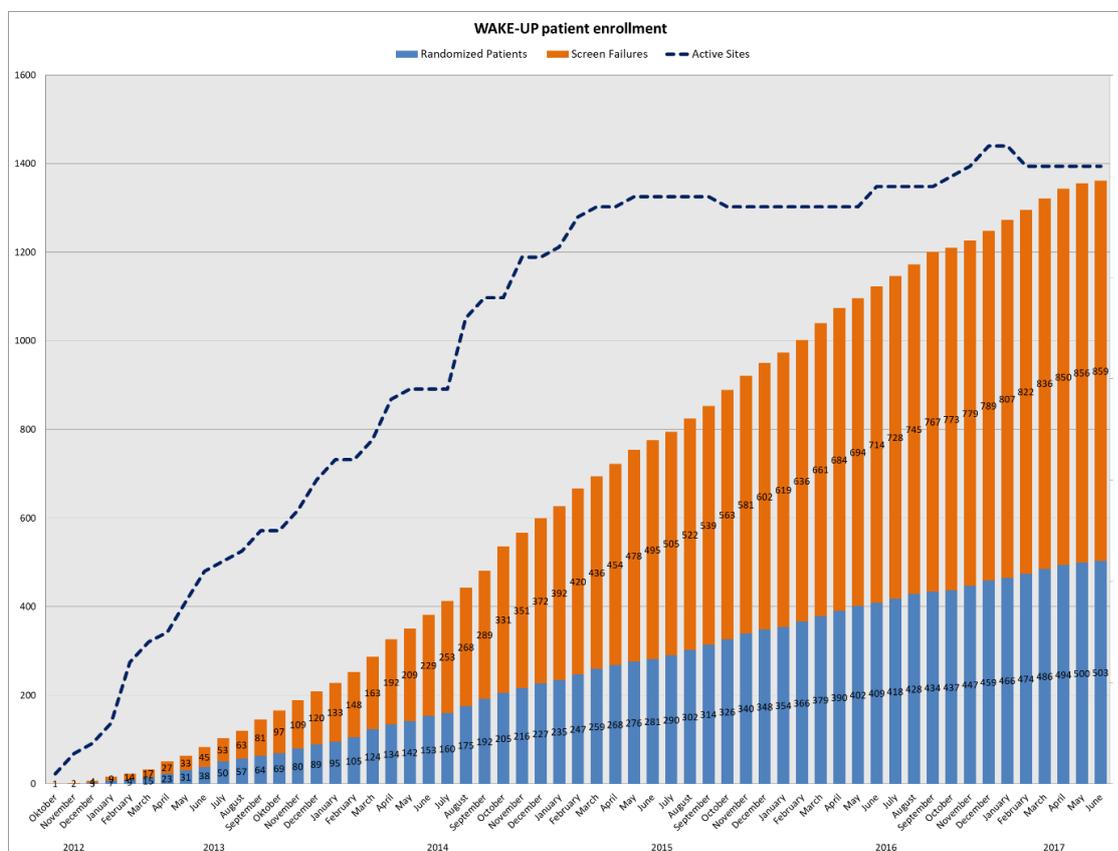


Figure 10: Active sites, patient enrolment, and patient randomization by the end of the trial

With the published positive trials of stroke thrombectomy in 2015, the steering committee discussed possible implications of these results on WAKE-UP. After thorough evaluation of all available data, the Steering Committee unanimously agreed that the WAKE-UP trial should be continued without any modification of the protocol, and investigators should continue enrolling and randomizing patients into WAKE-UP irrespective of vessel occlusion including large vessel occlusions. This decision was based on advice from the external Scientific Advisory Board and the Data and Safety Monitoring Board. Following their meeting on April 2, 2015 the DSMB concluded: “The committee considered that despite the recent publications on thrombectomy, the study should carry on without modification of the protocol.” This is also in line with recent recommendation by experts from the European Stroke Organisation (ESO), the European Society for Minimally Invasive Neurological Therapy (ESMINT), and the European Society of Neuroradiology (ESNR) during the ESO-Karolinska Stroke Update in November 2014. In the resulting Consensus statement on mechanical thrombectomy, they clearly recommend further trials addressing further open issues, which apply to the target population of WAKE-UP: “It is encouraged to perform and include patients in RCT addressing unresolved thrombectomy questions such as ...treatment in a late und unknown time windows...”.

Enrollment in the clinical trial was below the original expectations and plans. Thus, the steering committee launched several corrective actions to improve enrollment. Finally, in 2015, the General Assembly decided to request a cost-neutral extension of the WAKE-UP project for additional 12 months in order to be able to successfully complete the clinical trial, which represents the core of the project. Together with the extension of the trial period, an extension of the trial to new countries (Austria and Netherlands) was decided resulting in an increase of the number of active study sites. A request for an amendment (No. 3) to the Grant Agreement was sent to the EC on 17.12.2015 and was approved by the EC.

In June 2017, the steering committee finally decided to stop enrollment in the trial although the originally planned sample size of $n=800$ patients was not reached. In an earlier meeting scenarios for successful completion of the project were critically discussed. However, without further funding and in the context of endovascular stroke treatment (thrombectomy) becoming more and more standard of care even for stroke with unknown symptom onset, i.e. the population targeted by WAKE-UP, randomization of further 300 patients within a reasonable time-period was not judged to be possible. Moreover, the overall appraisal was that given the rather conservative treatment effect estimates that were made for sample size calculation, with more than 500 patients randomized the trial should have sufficient power to demonstrate a beneficial treatment effect.

The decision to stop enrolment was communicated to all sites, and enrollment in the trial was effectively stopped by 30 June 2017. The final outcome evaluation of the last patient was performed on 21 September 2017 (“Last patient out”). By the end of the trial, 1362 patients were enrolled in the trial, of whom 503 were randomized and 859 were screen failures.

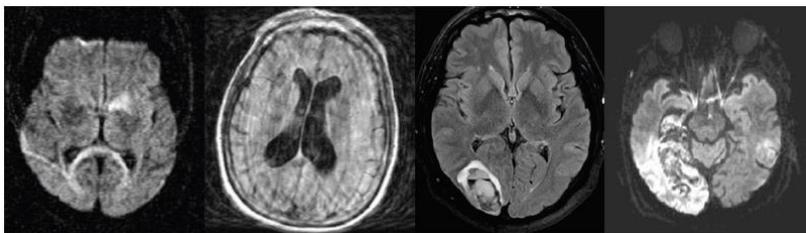
In the following months, monitoring activities and data management were completed. By the end of the project period, the database is ready for being locked and the final analysis will be prepared in February 2018. Scientific presentation of the trial results is already scheduled for the large clinical trials session at the European Stroke Organisation Conference (ESOC) in May 2018 in Gothenburg.

Image processing algorithm optimisation and software development (WP 07)

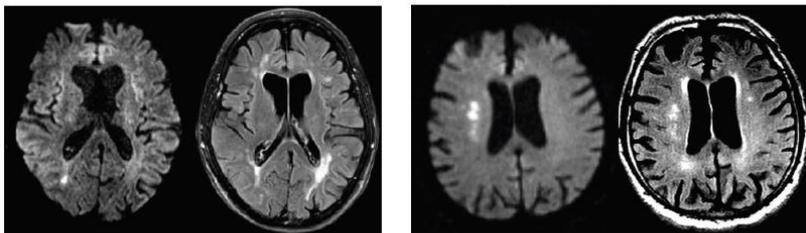
Within the WAKE-UP project, two software components for brain image analysis were developed. The Radiology Trainer allows for training and certifying the readers within the WAKE-UP study. The Stroke Quantification Tool SONIA enables one to process and quantify FLAIR and DWI image data and to quantify several important features like mean stroke intensities, FLAIR ratios, ADC ratios, brain volume, CSF volume.

Radiology trainer

Fraunhofer MEVIS implemented a software tool which is used a training platform for all people who intend to participate in the WAKE-UP study. The idea of this tool is to guarantee that all participating radiologist or neurologists have the same high level of knowledge regarding the inclusion and exclusion criteria in this study. FME integrated 65 data sets from the PRE-FLAIR study in the software tool, arranged into 5 sets consisting of 13 different cases. The tool also includes a trainings mode where feedback is given directly after filling out the electronic case report form (eCRF). Afterwards, each participant has the possibility to perform an examination consisting of 13 different cases. The results can be electronically send to FME which sends back the feedback within one week. A check sum ensures an option to find out if the users email for sending the report and the email used in exam report generation do not agree. The encoded results make use of the users email as well as the time point of saving, in order to avoid reusing results by other readers to pass the exam.



Poor DWI / FLAIR quality (movement?) / bleeding / extended infarct



Leukoaraiosis near lesion / FLAIR positive lesion

Figure 11: Examples of cases to be excluded

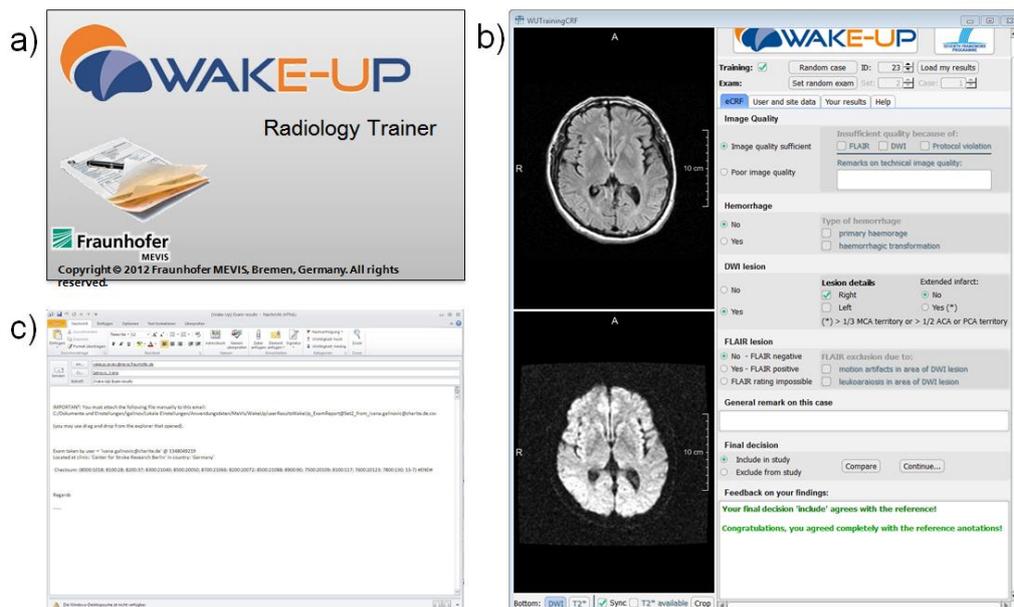


Figure 12: Screenshots showing the WAKE-UP radiology trainer. a) start up screen, b) eCRF which has to be filled out corresponding to the presented FLAIR and DWI images. c) If in the examination mode all 13 cases has

been answered, the final result can be sent via email to FME. The results are automatically encoded as an attachment and the email browser automatically generated an email. The only thing, the user has to do is to press the send button in the email client.

Stroke Quantification Tool (Sonia)

The Stroke Quantification Tool (Sonia) has been developed by Fraunhofer MEVIS for the efficient and reliable quantification of stroke MRI data and will allow physicians to integrate the knowledge of leading stroke imaging experts into their individual treatment decisions in real-time. The tool makes stroke MRI analysis quicker, more reliable and more effective across knowledge borders and infrastructural boundaries. The incorporation of multiparametric imaging into acute treatment decisions leads a step further towards personalized medicine and improved treatment outcomes. The basic idea behind the tool is to allow for a quantitative comparison between the areas of segmented lesions and the segmentations achieved by mirroring the lesions along the medial longitudinal fissure.

The tool is able to import and process DICOM data. The import process will take less time and the list of imported data sets might be decreased if there are also other sequences available for the case like perfusion, CT, and so on, see Figure 13.

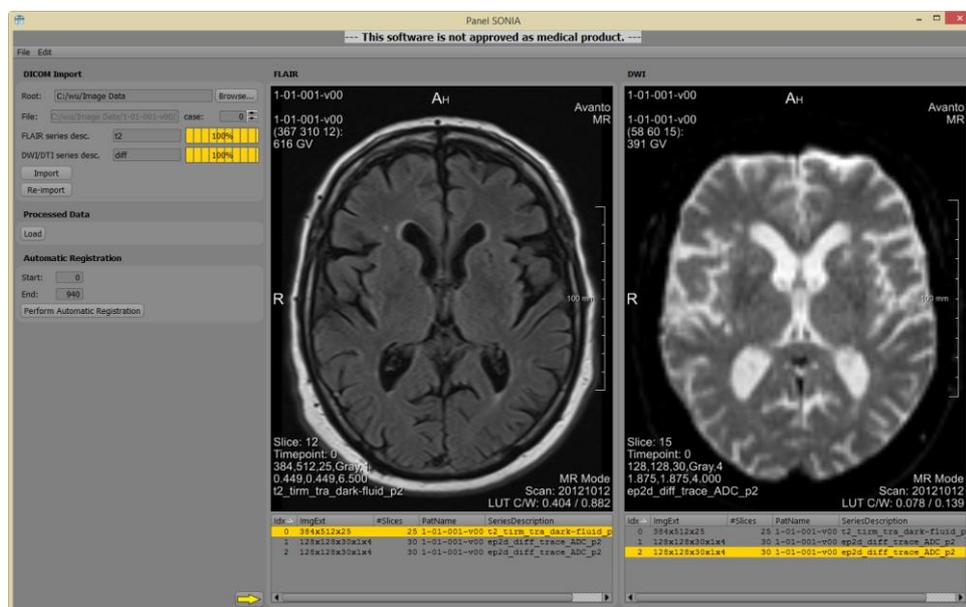


Figure 13: If there is more than one sequence available which fits to the series description, you have to select the correct DWI and FLAIR data in the list below the displayed data.

A rigid registration with NGF similarity measure is used for the registration of the FLAIR and DWI data. In addition, deformable registration of all data sets to the MNI 152 atlas has been implemented for detailed quantitative analysis with respect to certain brain regions.

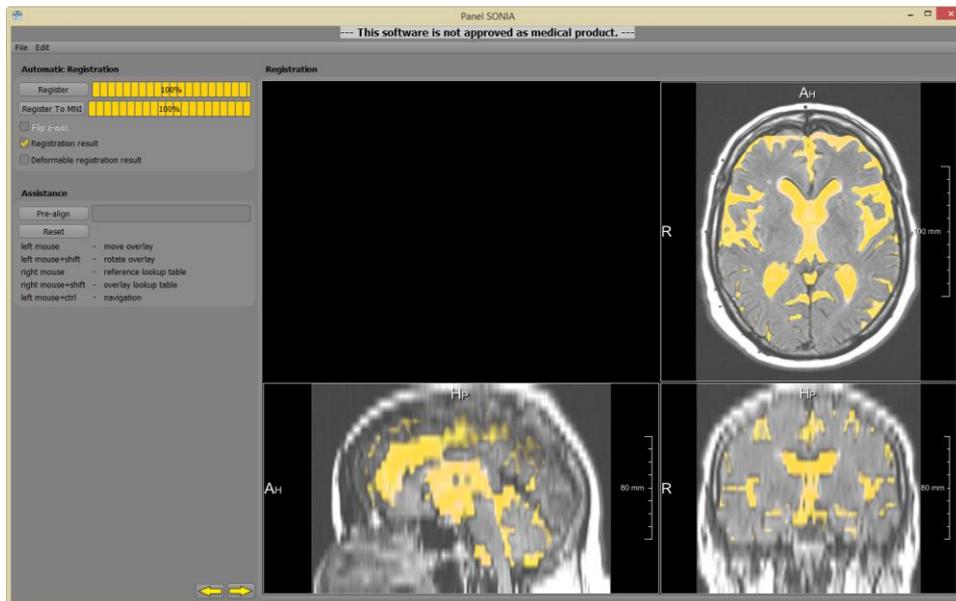


Figure 14: A good registration ensures reliable and precise quantification results.

If having DWI data, the diffusion images are stored at different time points in the data set. Usually, the time points are automatically detected. If the detection fails, one can manually adjust them, see Figure 15.

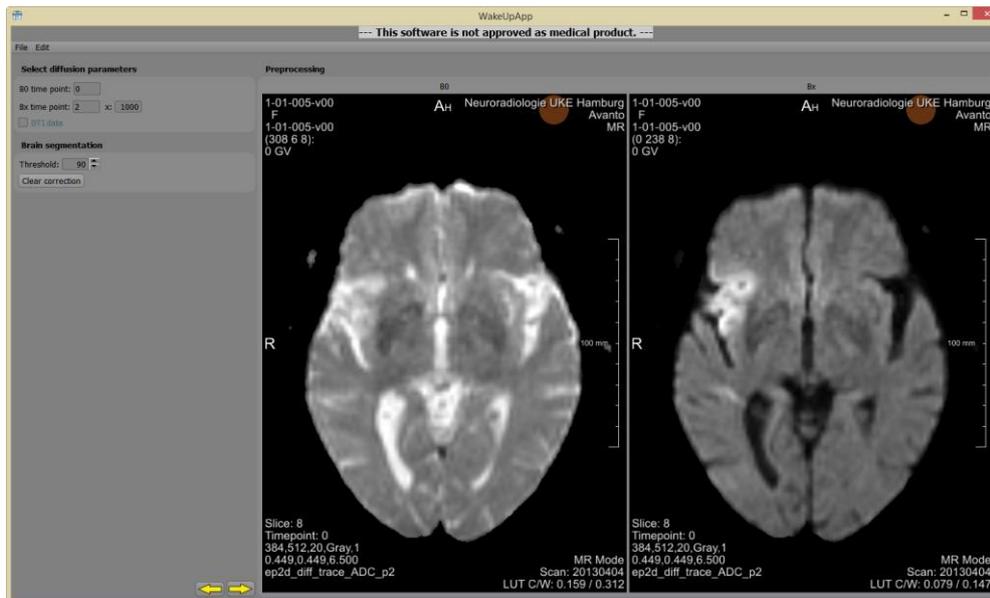


Figure 15: From the B_0 image (left) and the B_{1000} image (right), the ADC map is calculated.

If having selected the correct diffusion parameters, the brain can be segmented by a threshold-based technique. The larger the threshold, the more skull is stripped from the brain. However, if the threshold is chosen too large, then holes will appear within the brain.

After having selected an appropriate threshold, remaining noise/skull can be removed manually.

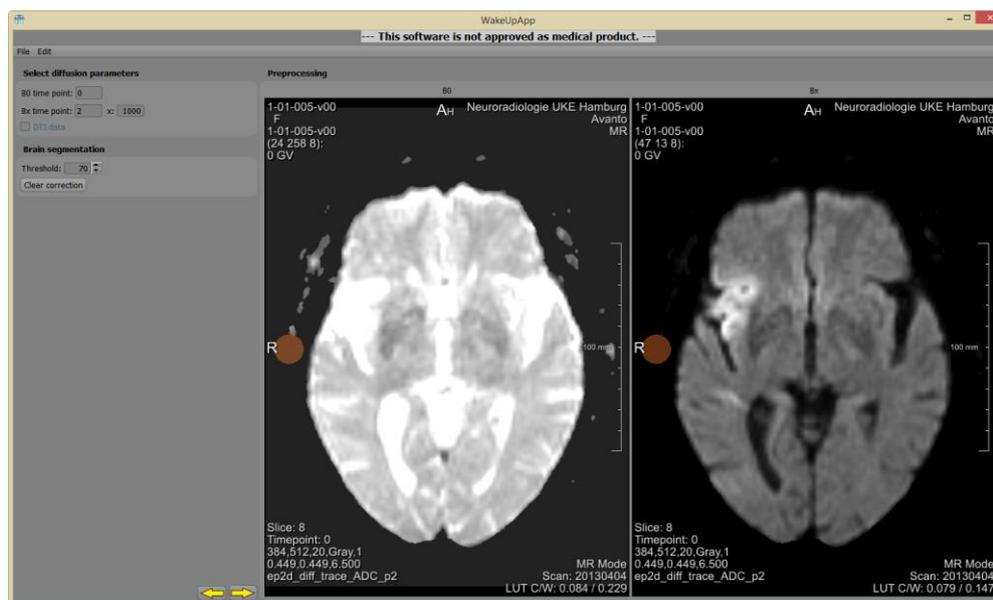


Figure 16: A threshold-based technique removes the skull and noise. If there are remaining parts, they can be removed manually as demonstrated here.

The quantification consists out of two main steps: first, the definition of the mid-sagittal plane, and second, the segmentation of lesions and their automatic mirroring. For the segmentation, all pixels within a region of interest (ROI) are segmented that have an ADC value of at most 620. In addition, slices below and above the ROI are also considered. The number of influencing slices and further parameters can be adjusted. Alternatively, all pixel values within ROIs can be quantified.

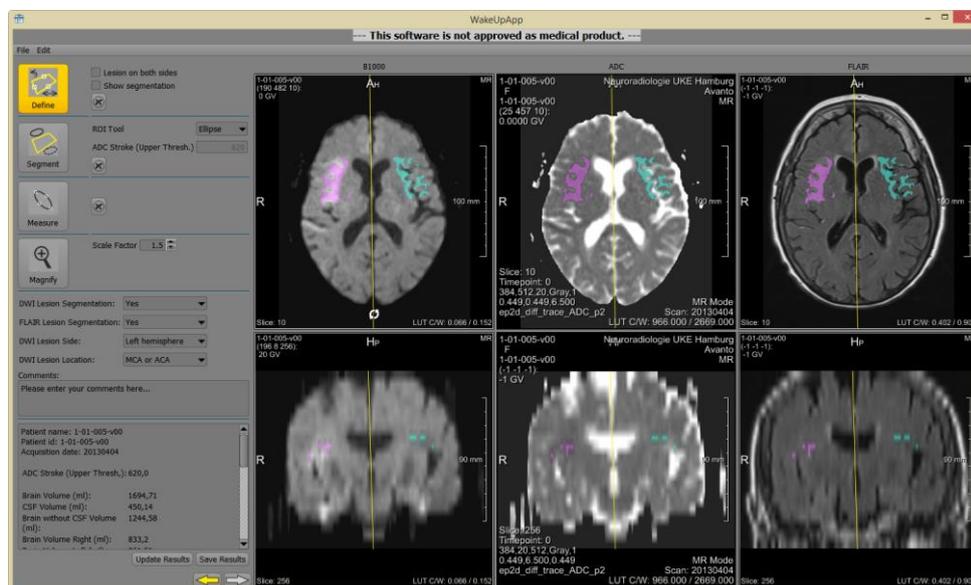


Figure 17: The quantification consists out of two interactive steps: the definition of the mid-sagittal plane by three markers and the delineation of the lesions by a region of interest (ROI).

Evaluation of treatment multiparametric MRI to predict treatment response (WP 08)

WAKE-UP used the DWI-FLAIR-mismatch pattern as imaging surrogate marker of ischemic lesion age in order to identify patients with ischemic stroke <4.5 hours making them likely to respond to thrombolysis. There are, however, competing approaches using MRI to identify patients likely to benefit from reperfusion treatment. These comprise the “penumbral” MRI pattern, defined by perfusion-diffusion-mismatch, and approaches focusing on the detection

of a brain vessel occlusion. The acquisition of MRI angiography data capturing brain vessel status as a mandatory part of the WAKE-UP imaging protocol, and the use of perfusion MRI in a large subset of study patients will enable us to validate these imaging approaches with regards to the prediction of treatment response. These analyses have been prepared during the project period and will be completed immediately after the primary analysis of the trial has been done.

An imaging database for scientific image analysis has been established and all MR images being part of the extended MRI protocol have been identified, sorted, and checked for quality and completeness. On the basis of this preparatory analysis, a workflow was developed for future scientific analysis of images. Preparatory analysis steps have been made including the segmentation of ischemic lesions. Overall, raw perfusion data are available for 366 of all enrolled patients.

To perform analysis of perfusion-diffusion mismatch according to the currently most widely used protocol, the RAPID software was obtained and the analysis of all DWI/PWI scans using the RAPID analysis pipeline was initiated.

Numerous ancillary scientific subprojects based on the data obtained in the WAKE UP trial have been proposed and discussed within the consortium and final approved by the project steering committee.

Finally, pooling of trial data with other MRI based trials of stroke thrombolysis (i.e. MR WITNESS, ECASS-4/EXTEND, THAWS) was approved and will be started, after the primary analyses of the trial have been completed.

Dissemination, transfer, scientific data sharing (WP 09)

The dissemination work package was led by participant 07 (K. Muir, UG) who is member of European and national stroke associations, guideline-writing groups, councils and advisory boards of neurological and stroke associations. All scientific partners were involved in this work package, building a consortium of renowned, highly interconnected stroke scientists, who bring their national and European connections to the relevant boards and committees. The Stroke Alliance for Europe (SAFE) was also extensively involved and played a major role in the dissemination of information to the public, using the existing network of SAFE member associations.

In order to ensure knowledge sharing and dissemination of the results achieved in the various stages of the project, WAKE-UP has adopted a “multimodal” dissemination approach that addresses the wide spectrum of stakeholders involved in the clinical trial. The major focus of its dissemination framework was to ensure that the project’s research and practical outcomes are widely disseminated to the appropriate target communities, at appropriate times using the most effective methods. Therefore, several ways and channels of dissemination have been used throughout the project, e.g.:

- Oral presentations at several scientific and public events
- Dissemination booth at the European Stroke Organisation Conferences in order to inform about the project and the current status of the research
- Regular newsletters
- Updates on the website, project flyer, twitter
- Videos in order to inform about the project (YouTube Channel and links on the website)
- Scientific publications using baseline data from the trial population

The final results of the WAKE-UP project will have a major impact on the treatment of acute stroke by changing clinical practice in the European Union through the publication of first class evidence from a large randomised controlled clinical trial. To ensure this, the results of WAKE-UP will require dissemination to both the public and in the scientific communities, especially targeting the decision-makers in international, European and national stroke

associations and guideline writing groups. This will be assured by the clinical and scientific profiles of the WAKE-UP partners. Even if results are not clearly supportive of benefit, the WAKE-UP project is expected to have importance to the medical community and will inform the design of further studies in this large group of patients for whom treatment options are presently limited.

Further details regarding the dissemination plan have been described in the deliverable report for D09.03.

Project Management (WP 10)

WAKE-UP consists of 10 work packages. For every work package a leader is responsible for carrying out the tasks as described in the DoW and to achieve the relevant goals. The project management has set up an effective communication infrastructure and fostered the integrative process within the consortium. By this, they ensured that all relevant information has been distributed to the responsible persons and supported them to achieve the objectives, complete the milestones in time and deliver the deliverables.

Additionally, they made sure that the consortium's contractual duties are carried out (gave advice in order to comply with the EU regulations and their contractual and legal requirements). The project management was also responsible for the financial controlling within the project and the preparation of the annual reporting to the European Commission as well as the organization of the bi-annual meetings.

1.4 Potential impact and main dissemination activities and exploitation of results

WAKE-UP addresses a massive and growing health problem in the EU and will provide a manifest benefit for individual patients, doctors involved in the management of stroke, and the society at large. Stroke is the 2nd most common single cause of death and the most frequent cause of permanent disability in industrialised countries. Estimated 2 million people per year are hospitalized for stroke in the EU, including estimated 400.000 people with wake-up stroke. WAKE-UP will provide effective treatment options to large numbers of patients currently excluded from any specific acute stroke treatment. The clinical trial represents the core of the project. This trial is designed to provide evidence of efficacy and safety of MRI-based thrombolysis in stroke patients with unknown time of symptom onset. By this, WAKE-UP will provide an effective treatment for a large group of patients currently condemned to the natural course of the disease.

Translate scientific advancement into clinical practice opening new treatment options

During the past decades enormous advances have been made in understanding the pathophysiology of stroke and in improving the diagnostic and treatment of acute stroke. Stroke MRI has revolutionised acute stroke imaging with diffusion weighted imaging allowing for the highly sensitive detection of acute ischemic lesion within minutes from onset. Randomised controlled trials have provided evidence for effective acute stroke treatment, and thrombolysis has been established as standard of care for acute ischemic stroke dramatically increasing the number of patients surviving stroke without disabling neurological symptoms. However, a population as large as 20% of acute stroke patients has been excluded from major parts of this progress, i.e. patients waking up with stroke symptoms. Patients with wake up stroke have been excluded from virtually all randomised controlled acute stroke trials, and they are excluded from treatment with thrombolysis as to approval criteria and national and international guidelines. WAKE-UP will turn the focus on these patients and translate the scientific progress made in basic studies into tangible clinical benefits by providing the benefit of acute stroke thrombolysis to this large population.

Establish a new standard of acute stroke image evaluation

Should the WAKE-UP trial have a positive outcome, it can be assumed that the therein tested imaging criterion of DWI-FLAIR mismatch will gain widespread acceptance in the neuroradiological community and eventually become a routine part of image assessment in patients with acute ischemic stroke of unknown onset. It will become necessary to train medical professionals (chiefly radiologists) to correctly interpret this MRI based sign. To this extent, the web-based training tool designed for the WAKE-UP study can be further expanded with additional explanations, imaging examples and/or test cases and subsequently made available to the public.

Provide new insights into the clinical picture of “wake-up stroke”

The WAKE-UP trial comprises the largest cohort of patients with unknown onset stroke studied by modern brain imaging as yet. Even prior to completion of the trial and the availability of the final results, analysis of the baseline data of the first thousand patients enrolled has provided valuable insights into clinical characteristics of wake-up stroke patients. Almost half of the patients with unknown time of symptom onset stroke were eligible for thrombolysis had MRI findings making them likely to be within a time window for safe and effective thrombolysis. This further strengthens the need for effective treatment for this group of patients. Of note, patients with daytime onset unwitnessed stroke differ from wake-up stroke patients with regards to clinical characteristics, but both groups are comparable in terms of MRI characteristics of lesion age. Thus, effective acute treatment based on the use of MRI as surrogate of lesion age might be suitable for patients with unknown time of symptom onset no matter for which reason time of symptom onset is unknown. These findings are novel and will impact the guidance of acute stroke treatment. The analysis was published in *Stroke*: Thomalla et al. Stroke With Unknown Time of Symptom Onset: Baseline Clinical and Magnetic Resonance Imaging Data of the First Thousand Patients in WAKE-UP (Efficacy and Safety of MRI-Based Thrombolysis in Wake-Up Stroke: A Randomized, Doubleblind, Placebo-Controlled Trial). *Stroke*. 2017;48:770-773.

Advance the understanding of MRI as surrogate marker of stroke lesion age

The DWI-FLAIR mismatch is a novel MRI-based concept of identifying acute ischemic stroke patients with acute ischemic lesions likely to be within the time window for intravenous thrombolysis (i.e. <4.5 hours of symptom onset). WAKE-UP has provided the first experience with this novel imaging concept in a large prospective cohort of stroke patients and by this has contributed to a better understanding of potential clinical cofounders of this imaging parameter. In an analysis of the first thousand patients enrolled in the trial, there were only minor differences in measured clinical characteristics between unknown symptom onset stroke patients with and without DWI-FLAIR mismatch. These findings demonstrate that DWI-FLAIR mismatch as an indicator of stroke onset within 4.5 h shows no relevant association with commonly collected clinical characteristics of stroke patients and confirms the use of this imaging pattern as surrogate biomarker of lesion age. These findings were published in the *International Journal of Stroke*: Thomalla et al. Clinical characteristics of unknown symptom onset stroke patients with and without diffusion-weighted imaging and fluid-attenuated inversion recovery mismatch. *Int J Stroke*. 2018 Jan;13:66-73.

Promote the concept of MRI guided treatment of unknown-onset stroke

The WAKE-UP project and especially the clinical trial has received remarkable attention in the international scientific community as well as in the public. The scientific publication of the study protocol in the *International Journal of Stroke* (Thomalla et al. A multicenter, randomized, double-blind, placebo-controlled trial to test efficacy and safety of magnetic resonance imaging-based thrombolysis in wake-up stroke [WAKE-UP]. *Int J Stroke*. 2014;9:829-36) has been cited 58 times since its publication in August 2014.

The concept of WAKE-UP is referred to in a growing number of scientific publications, and the increasing number of citations of these articles reflects the increasing awareness to the concept in the scientific community (see Figure 18). THE DWI-FLAIR mismatch concept and the WAKE-UP trial is also referred to in neurological and neuroradiological textbooks. The start and progress of WAKE-UP has been covered in numerous contributions in newspapers, journals, and TV contributions.

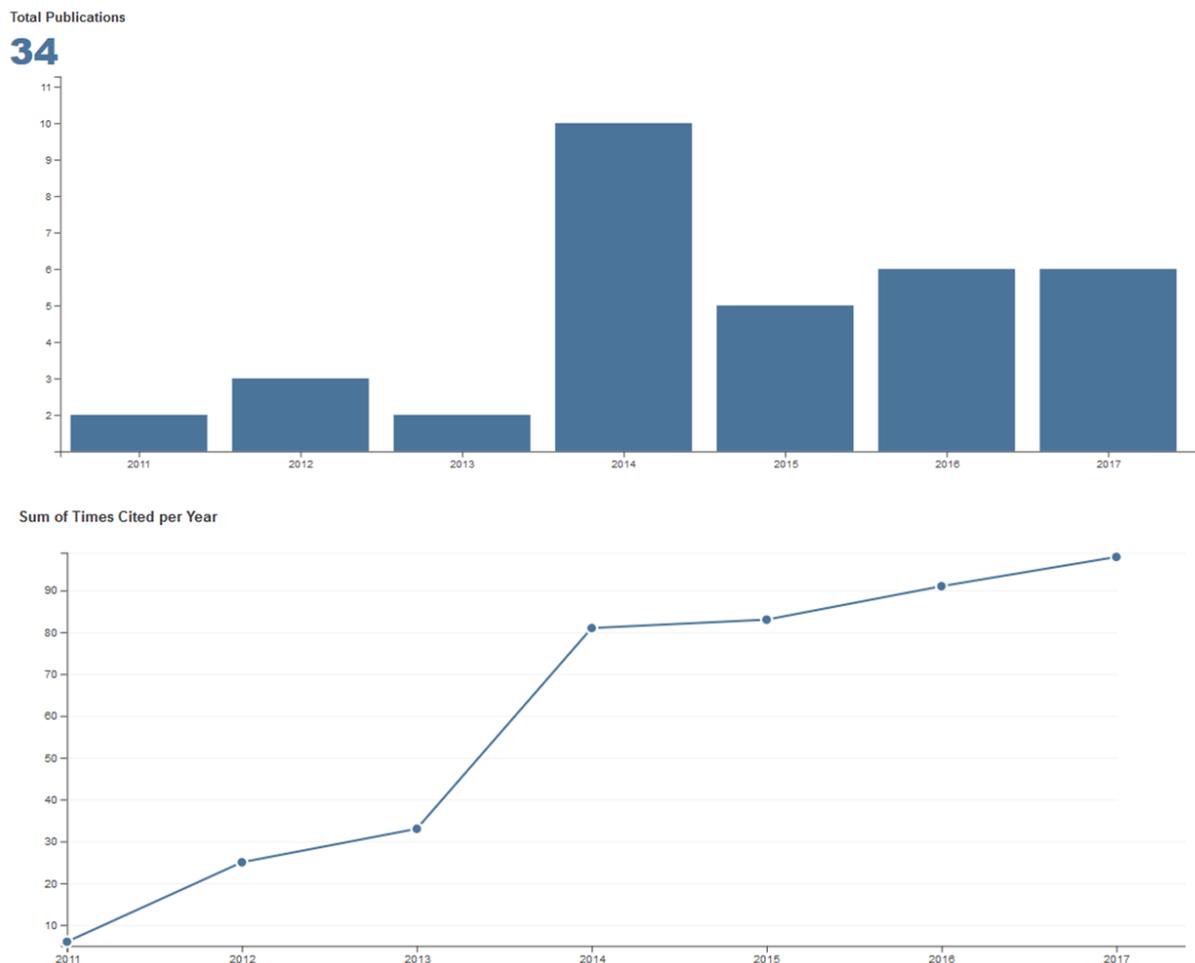


Figure 18: Scientific publications referring to the “DWI-FLAIR mismatch” concept (upper) and growing number of citations of articles referring to the “DWI-FLAIR mismatch” concept (lower). From the Web of Science (ISI Web of Knowledge), <https://clarivate.com/products/web-of-science/>

Dissemination activities in WAKE-UP have promoted the concept of MRI guided treatment of unknown-onset stroke applying the easy-to-use DWI-FLAIR mismatch concept in clinical practice. This is reflected by a growing number of reports of MRI-based treatment of wake-up stroke within either intravenous thrombolysis or mechanical thrombectomy using the imaging concept of WAKE-UP even before the results of the trial being available:

- Escalard et al. ETIS (Endovascular Treatment in Ischemic Stroke) Research Investigators. Unknown-Onset Strokes with Anterior Circulation Occlusion treated by Thrombectomy after DWI-FLAIR Mismatch Selection. *Eur J Neurol*. 2018 Jan 21. doi: 10.1111/ene.13580. [Epub ahead of print]
- Wei et al. MRI based thrombolysis for FLAIR-negative stroke patients within 4.5-6h after symptom onset. *J Neurol Sci*. 2017 Jan 15;372:421-427.
- Mourand et al. Favorable Bridging Therapy Based on DWI-FLAIR Mismatch in Patients with Unclear-Onset Stroke. *AJNR Am J Neuroradiol*. 2016 Jan;37(1):88-93.

- Jeong et al. Diffusion-weighted imaging-fluid-attenuated inversion recovery mismatch is associated with better neurologic response to intravenous thrombolytic therapy in acute ischemic stroke patients. *Clin Exp Emerg Med.* 2015 Mar 31;2(1):31-37.

Aoki et al. Intravenous thrombolysis based on diffusion-weighted imaging and fluid-attenuated inversion recovery mismatch in acute stroke patients with unknown onset time. *Cerebrovasc Dis.* 2011;31(5):435-41.

Develop approaches for more effective execution of clinical stroke trials

In WAKE-UP, we had to face the challenge of a randomized trial requiring informed consent from all participants, while acting under pressure of time and addressing patients suffering from stroke symptoms that frequently interfere with the capacity to give consent. We developed a pragmatic and effective comprehensive approach to overcome this problem while being full in line with European and national legislation and fundamental ethical principles of research involving humans. The workflow of obtaining informed consent developed in WAKE-UP has proven feasible and effective and has been copied by subsequent European multicenter randomized trials, such as PRECIOUS (PREvention of Complications to Improve OUTcome in elderly patients with acute Stroke. Rationale and design of a randomised, open, phase III, clinical trial with blinded outcome assessment, registered with ISRCTN, ISRCTN82217627, funded by the EU under GA No. 634809) and TENSION (Efficacy and safety of Thrombectomy iN Stroke with extended leSION and extended time window: a randomized controlled trial, ClinicalTrials.gov Identifier: NCT03094715, funded by the EU under GA No. 634809754649). The preparatory work of WAKEUP has supported a more effective start of these international clinical trials and will be available for adaption in future trials.



Figure 19: Both European multicenter randomized trials (PRECIOUS and TENSION) adopted the workflow of obtaining informed consent from WAKE-UP

A Japanese trial has adopted the concept of WAKE-UP, the Thrombolysis for Acute Wake-up and Unclear-onset Strokes With Alteplase at 0.6 mg/kg Trial (THAWS), except for treatment with a reduced dose of Alteplase as approved in Japan. We have made imaging standards and training material available to the THAWS investigators and by this enabled a quick start of the trial ensuring comparability of inclusion and exclusion criteria between both trials, THAWS and WAKE-UP.

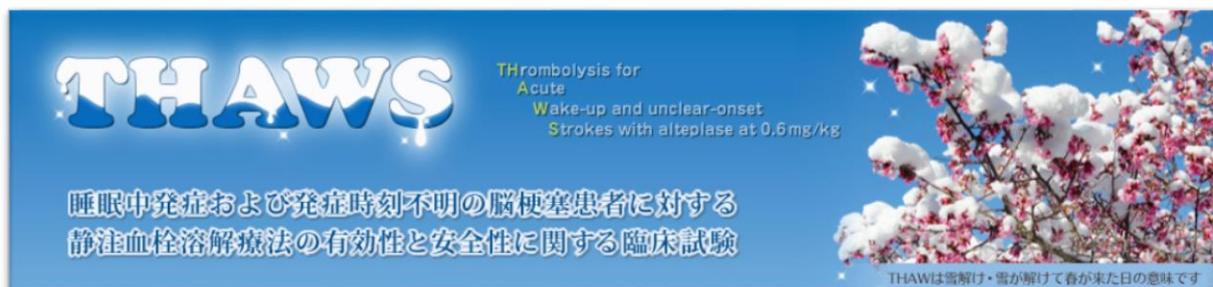


Figure 20: The Japanese THAWS trial has adopted the WAKE-UP concept (<https://thaws.stroke-ncvc.jp/>)

Proof of safety of MRI-based thrombolysis in unknown symptom onset stroke

While at the time of redaction, the main efficacy results of the trial are still unknown, and no unblinded analysis regarding the treatment groups is available, we already know from evaluation of the independent Data and Safety Monitoring Board (DSMB) based on grouped trial data that there were no safety issues in the clinical trial. Thus, we are already able to conclude that the treatment approach tested, i.e. MRI-based intravenous thrombolysis in patients with unknown time of symptom onset, is safe. This will support stroke physicians to consider thrombolysis in patients with unknown time of symptom onset based on individual evaluation of benefit and risk and thus may make effective reperfusion treatment available to these patients currently excluded from intravenous thrombolysis. Even if the final analysis will not demonstrate the efficacy of MRI-based thrombolysis for acute ischemic stroke patients with an unknown time of onset, WAKE-UP will have established the feasibility and safety of this treatment strategy.

Change guidelines and clinical practice of acute stroke treatment

Currently, there is no specific treatment recommendation for patients with wake-up stroke by European and national guidelines. The evidence provided by WAKE-UP will be brought into European and national guideline writing groups by the project partners and lead to changes of European and national guidelines. We expect guidelines for acute stroke management by the European Stroke Organisation (ESO) as well as those by national associations (e.g. Deutsche Schlaganfallgesellschaft, GER; The National Institute for Health and Clinical Excellence, GBR; Haute Autorité de Santé, FRA) to be changed immediately. The results of WAKE-UP will for the first time allow for the inclusion of specific treatment recommendations comprising thrombolysis for patients with unknown symptom onset, which will have a profound impact on clinical practice.

The results of WAKE-UP are expected to rapidly change everyday reality of clinical practice. There is a widespread awareness of and dissatisfaction with the lack of specific treatment options for patients with wake-up stroke. Given the increasing practice to perform thrombolysis in patients with wake-up stroke as an individual treatment option within the past years, we expect a positive trial to lead to an immediate change of clinical practice in stroke centres across the EU.

Reduce the burden of stroke-related disability

WAKE-UP was formed to cope with a major challenge of health care in the EU and to reduce the burden of stroke-related disability, both at an individual level and with regards to the socio-economic sequelae. Many survivors of stroke lose their ability to work or live independently resulting in severe personal and societal losses. WAKE-UP strives to reduce this burden by providing an effective treatment for a large group of patients currently condemned to the natural course of the disease. Estimated 2 million people per year are hospitalized for stroke in the EU, including estimated 400.000 people with wake-up stroke. Extrapolating data on clinical characteristics and imaging findings in wake-up stroke and on the frequency of other contraindications against thrombolysis, we estimate that 100.000 patients with wake-up stroke per year are potentially eligible for thrombolysis. Based on the observed treatment effect in previous stroke thrombolysis trials we expect thrombolysis to result in a 10% absolute increase of patients with a favourable outcome, which is defined by no or only minimal neurological symptoms being a highly relevant outcome for affected patients. Thus, WAKE-UP might help avert lasting neurological symptoms or disability in estimated more than 10.000 patients per year in the EU. The overall effect on outcome will even be larger, as novel endpoint analytic techniques have demonstrated that the number needed to treat (NNT) for 1 patient to improve in a clinical relevant manner number may be as low as 3.3 for intravenous thrombolysis. This translates into a number of >30.000 patients per year in the EU, which might benefit from the treatment approach provided by WAKE-UP in terms of a clinical relevant improvement.

Being the most frequent reason for adult onset disability, stroke accounts for an enormous socio-economic burden. The economic costs of stroke add up to more than € 34 billion in the EU in 2006. By reducing the number of disabled patients after stroke, the results of WAKE-UP will lead to a tangible decrease of follow-up costs of stroke.

Support harmonise and standardization of in EU and international

WAKE-UP will improve acute stroke treatment and change clinical practice following the European idea of harmonisation and standardisation of citizen's access to medical treatment across the EU. During the project period, diagnostic and treatment algorithms have been harmonized among all trial centers. As a result of dissemination activities and public discussions, the promoted treatment concept has reached far more stroke centers than those directly involved in the trial and by this already has influenced standards of acute stroke treatment within a wide range.

Encourage future research and innovations

WAKE-UP will encourage future research on acute stroke treatment guided by multiparametric stroke MRI. Analysis of imaging predictors of outcome in WAKE-UP will likely ignite subsequent studies. Pre-planned pooled analysis with other trials (e.g. ECASS-4/EXTEND, MR WITNESS, THAWS) trials will entail additional insights and further strengthen cooperation between European and international stroke research groups. This will set grounds for potential subsequent international investigator initiated clinical trials involving novel imaging techniques or novel drugs. WAKE-UP data will be shared with the Virtual International Stroke Trials Archive (VISTA) pursuing the idea of promoting excellence in stroke care and trial design by establishing a large and open resource of clinical and imaging data of stroke patients.

Strengthen European Competitiveness

Stroke research at the highest international level requires cross-linked multidisciplinary multinational collaboration between clinical experts, researches, industry, and politicians. WAKE-UP has brought together leading European stroke researchers and enterprises in a large scale cooperative network setting grounds for subsequent projects with profound impact on European competitiveness in the field of stroke research. Academic partners and SME have successfully cooperated in developing the WAKE-UP software tools giving an example of joining expertise from the academic and industrial background. Further exchange of knowledge between researchers, clinicians, and SME partners as initiated in the WAKE-UP consortium will strengthen clinical research and boost the innovative capacity of European health-related industries.

2. Use and dissemination of foreground

The list of all scientific (peer reviewed) publications relating to the foreground of the project and the list of all dissemination activities (publications, conferences, workshops, web sites/applications, press releases, flyers, articles published in the popular press, videos, media briefings, presentations, exhibitions, thesis, interviews, films, TV clips, posters) can be found in the Participant Portal.

Any applications for patents, trademarks, registered designs, etc. or any other exploitable foreground has not been relevant for WAKE-UP.

3. Report on societal implications

The questionnaire regarding statistics and indicators on societal and socio-economic issues addressed by projects has been filled in in the Participant Portal.