Biannual newsletter | **September 2025**

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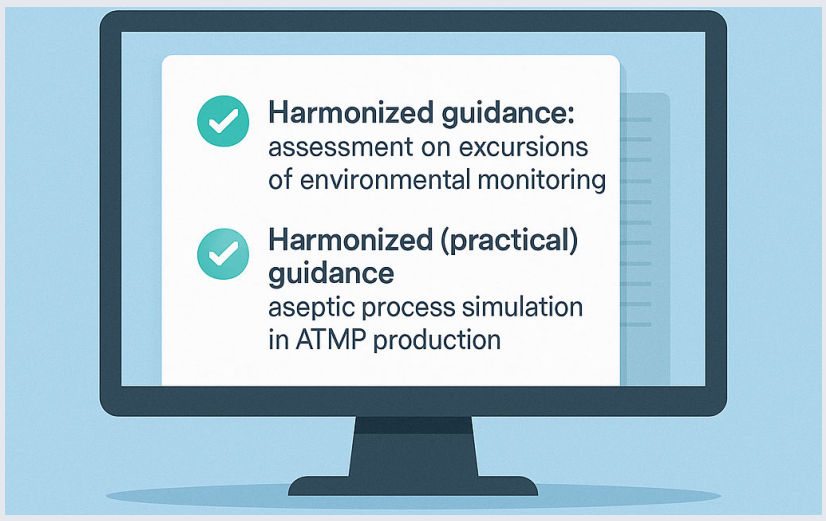
Two harmonized procedures



The second harmonized procedure was published by the DARE-NL WP2.3 team in June. Members can access the new procedure in Zenya: Harmonized (practical) guidance: aseptic process simulation in ATMP production (contact Adel (A.Medzikovic@umcutrecht.nl) if you have questions about Zenya licenses at your institute). Aseptic process simulation (APS), also known as media fill, tests whether the aseptic manufacturing procedure is adequate in preventing contamination of the product. An APS challenges not only the manufacturing procedures, but also other domains such as personnel, materials, equipment, environment. This new harmonized guidance can be used to support the design of an effective APS that complies with current regulatory guidelines, GMP for ATMP (2017) and relevant requirements of GMP Annex 1 (2022). Additionally, advise on bracketing and matrixing approach and intervention management are included in this guidance.
Written by Angela van Dorp (Erasmus MC) and Paul de Jonge (Radboudumc).

Follow these steps to implement harmonized procedures at your center:

- Send the document to all staff members
- Put the topic on the staff meeting agenda and discuss
- Check for potential improvements or gaps in your in-house documents
- Take the document up as a reference

Writers of the procedures have become experts on the topic and provide trainings on request. Anouk Donners provided an expert training on the ‘Harmonized practical guidance: assessment on excursions of environmental monitoring’ to operators during the operator workshop on 24 March. Members can find the training attached to the document, so all experts can provide the training upon request. Reach out if you are interested in a training on either of the harmonized procedures.

DARE-NL ANNUAL CONSORTIUM MEETING 2025

On 19 September, the DARE-NL Annual Consortium Meeting took place at the Princess Máxima Center, welcoming 180 participants from across the ATMP field. With a diverse representation of organizations and fantastic speakers, the day was a great success — as you can see from the pictures.

The program was structured around three key sessions:

1. Navigating regulation to patient access – addressing the hospital exemption pathway and the EU HTA regulation
2. Bridging the gap to clinical practice together – highlighting initiatives and strategic partnerships needed to advance ATMPs
3. Breaking barriers from innovation to patient access – exploring developments in manufacturing and clinical implementation

Throughout the day, leading experts shared valuable insights into how we can accelerate patient access to ATMPs. In addition, the interactive break-out session and sponsor demonstrations provided participants with opportunities to engage with key opinion leaders, cutting-edge technologies and discuss new developments in the field.

For DARE-NL members, presentation slides and the summary of the evaluation meeting are now available online. If you attended, please don't forget to share your input via the feedback survey — your perspective is crucial for shaping future editions.

Planning for next year's meeting is already underway, and we look forward to welcoming you again. Stay tuned for updates!

DARE-NL PROJECT HIGHLIGHTS

WP1: Setup of DARE-NL data, training and valorization platform

Lead: Emma de Pater, Erasmus Medical Center

Adel Medzikovic started as Quality Officer at the UMCU on 1 August – welcome to the team Adel!
This means you can now direct all your questions and requests regarding the DARE-NL website, Zenya and Teams environment to A.Medzikovic@umcutrecht.nl.
One of the first things he did was launch the **DARE-NL LinkedIn page** – follow us to stay up to date on the latest developments in the Dutch ATMP field.

ATMP education

The **operator workshop** on 24 March was very successful with 72 operators across the DARE-NL partners attending. The majority of participants (80% of 41 respondents) reported a ≥2-score improvement in their understanding of practices in other centers and half identified improvement in their ATMP knowledge. Find the program and pictures here. Planning of the next edition has initiated – let us know if you have any suggestions for the content!

A partnership of universities of applied sciences, including our partner in education Hogeschool Avans, has received a grant from the European Institute of Innovation and Technology to further integrate cell and gene therapies in education. Among other things, teach-the-teacher workshops will be implemented this fall, with an approach similar to the DARE-NL operator workshop: plenary presentations followed by break-out sessions for substantive discussions with lecturers from the universities of applied sciences.

A **workshop on recurring challenges in CCMO and CTIS reviews** for ATMP trials will take place at the Erasmus MC on 30 October. We will discuss common feedback and share practical tips. The workshop is followed by a meeting of the ATMP working party.

WP2: Harmonizing GMP processes for the manufacturing of cancer-specific ATMPs

Lead: Trudy Straetemans, University Medical Center Utrecht

Harmonization of GMP procedures (WP2.3)
As mentioned above, the first two **harmonized procedures** have been published and are accessible to all member institutes, including training documentation. The third harmonized procedure on the validation of closed, automated culture systems is in development.
Implementation in local practice is ongoing at partner institutes, with a proactive approach initiated by multiple partners. A training to operators of partner institutes was given on March 24th as part of the implementation of the first published procedure.

Manufacturing procedures and digital batch record systems (WP2.4)
Currently used and known digital batch record systems have been inventoried (for members see Inventory of software systems.docx). A user requirement specification for **batch record software** is under development, including demonstrations by different providers.

A **registry data** production task force has been established in collaboration with the Oncode Accelerator Cell and Gene therapy workstream. The first aim of the task force is to align existing registries by making an inventory of existing partner production registries, followed by a discussion on best collection practices and which production set(s) to share. This nicely aligns with the organization of a trial registry symposium (WP1/6, 29 January 2026), where collaboration partners are invited to share insights for the joint creation of an optimal registry setup.

WP3: QC harmonization and assay development

Lead: Inge Jedema, NKI/AVL

Development and implementation of QC assays is ongoing (WP3.1/3.2)
The overview of assays has been shared in the DARE-NL Teams environment (accessible for members: 2023-11-14 Overview QC assays.pptx). This overview is used as a basis for the selection of assays to be implemented at DARE-NL partner sites and/or joined validation by DARE-NL partners.

Validation of **cell counting methods** according to the new EP2.7.29 guideline using round robin tests is ongoing. In-house mycoplasma testing (based on ddPCR) and sterility testing (BactAlert) are implemented at the NKI.

Inventory of QC requirements in the EU, USA, and UK is ongoing (WP3.3)
Interactions with EMA on specific QC assays (incl potency) for ATMPs are ongoing (e.g. as part of an ongoing MAA procedure NKI and exploratory advice meetings with CBG/EMA for other ATMPs by DARE-NL partners) and shared in DARE-NL.

WP4: Setup of a Dutch academic GMP vector manufacturing platform

Lead: Edwin Bremer, University Medical Center Groningen

Lentiviral production platform is under development (WP4.1/4.5)

The GMP-grade Master Cell Bank is currently being produced, for subsequent use in the manufacture of the first clinical-grade LV batch. The upstream and downstream processes have been defined at pre-GMP stage and tech-transfer is ongoing to initiate the first GMP-grade lentiviral batch (of the ligand-based CAR UMCG-001 for T-ALL) as 'demonstrator' project in Q4 of 2025. Edwin Bremer was recently awarded €2.2 million by KWF to launch a **clinical trial with CAR-T cells** engineered with this DARE-NL vector. Enrollment of patients with CD7-positive hematological malignancies is expected to start mid 2026.

The **pDARE-NL transfer plasmid** with FTO has already been shared with several of the DARE-NL institutes along with pre-GMP manufacturing SOPs to facilitate harmonization of preclinical research with GMP procedures for rapid tech-transfer of academic lentivirus-based ATMPs.

Successful establishment of GMP-ready retroviral production platform (WP4.2)
For the retroviral platform, a stable producer cell line has been successfully developed in-house and **RV manufacturing** has been successfully upscaled.

WP5: Identification and implementation of new technologies for the development and GMP-compliant manufacturing of ATMPs

Lead: Harry Dolstra, Radboud University Medical Center

Roadmap for new technologies implementation is under development (WP5.1)
A taskforce has been setup to tackle the roadmap for clinical translation and implementation of CRISPR technology. The taskforce is currently working on a practical guide aimed at supporting academic developers of *ex vivo* CRISPR-based GTMPs for first-in-human clinical trials.
Harry Dolstra participated in an expert meeting on *in vivo* gene editing hosted by the RSNN on 15 July, where engaged representatives from academia, industry, regulatory authorities, consultancy and patient organizations came together for an open dialogue. The goals of the expert meeting were to:
▪ Assess the existing regulatory frameworks applicable to *in vivo* gene editing
▪ Conduct a gap analysis: identifying where regulations fall short, particularly the gaps in (explicit) regulation during the transition from preclinical to clinical phases and access to the market.
▪ Formulate recommendations for the (further) development of appropriate and future-proof regulatory frameworks, based on recent scientific and technological insights.
A report summarizing key meeting insights and considerations will be shared with the Committee for Advanced Therapies (CAT) from the European Medicines Agency (EMA).

Route for manufacturing GMP-grade CRISPR-Cas is designed (WP5.2-5.4)
Production of GMP-grade HDR templates has been initiated at the NKI. The overall business case for CRISPR-Cas9 reagents is under development.

WP6: Regulation, health economics, health technology assessment and patient access

Lead: Pauline Meij, Leiden University Medical Center

Overview of manufacturing, evidence, HTA and regulatory pathways (WP6.1)
An updated version of the **database with approved** (MA) **ATMPs** and horizon scan with relevant patient organizations has recently been published (scroll to 'ATMPs assessed by the European Medicines Agency and in late development'). In addition, a pilot was initiated by the LUMC with FarmInform to collect ATMP data and combine and analyze that with the ATMP data FarmInform has from other (commercial) parties.

A **workshop with CCMO** is scheduled at the Erasmus MC on 30 October. The idea is to exchange common questions by CCMO and common obstacles ATMP developers encounter when submitting a study in CTIS. This is a workshop for partners – let me know if you would like to receive the invitation.

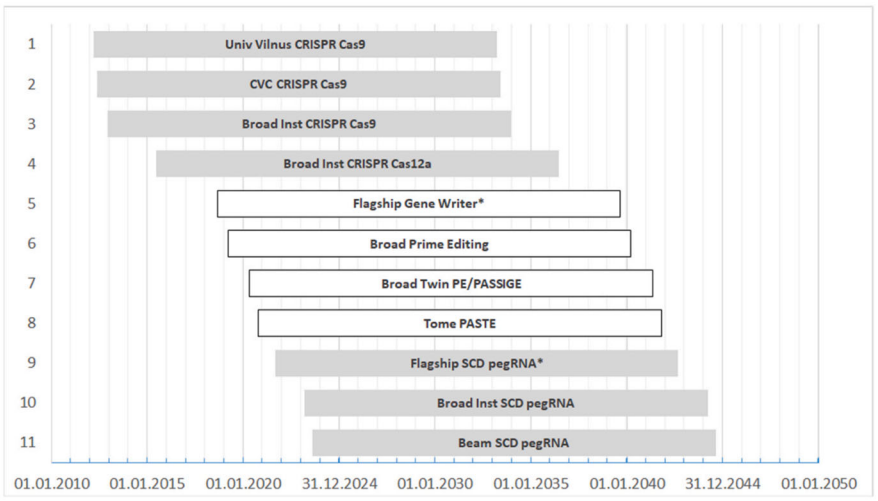
The TCR-T therapy product developed at the LUMC, also by Mara Tihaya in the DARE-NL Regulatory Affairs program, was presented at the fifth listen-and-learn focus group meeting of the EMA Quality Innovation Group on 8-9 April. The meeting report has been published.

Tool to assess academic CGT-specific development costs (WP6.2)
Cases are further developed based on the **costing tool** at the Erasmus MC, Radboudumc and LUMC. Three case studies have been identified for inclusion. The costing tool is currently undergoing updates/expansion.

An HE and trial registry for ATMPs are in development (WP6.4)
Do you have an interest in **ATMP clinical trial registries**? Then we invite you to join our trial registry symposium at the UMCU on 29 January 2026. Experts in the field will provide an overview of clinical trial databases and the basics of the new OMON registry. You can get guided hands-on experience with OMON and discuss expectations moving forward. All experts and stakeholders are invited to align the needs of as many stakeholders as possible. Find the program and registration form here.
This workshop nicely aligns with the registry data production task force setup in WP2.4, which will spread the invitation for broader reach and joint efforts toward setting up on optimal registry.

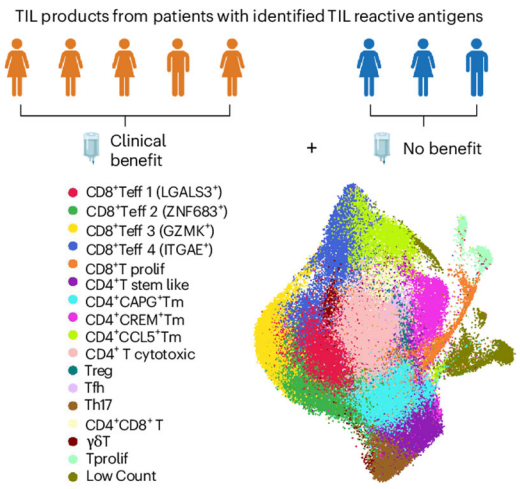
PUBLICATION HIGHLIGHTS IN THE FIELD OF ATMPS

After two overviews of CRISPR Cas9 and Cas12a patents in 2024, biologist and pattent attorney Ulrich Storz published an overview of **patents surrounding the prime editing and integrase-based variants**. While these techniques offer great promise for the precise integration of large DNA stretches into a host genome, it appears that a new chain of dependencies is about to unfold that makes the establishment of Freedom to Operate for interested parties complicated. The analysis covers a small spectrum of the IP landscape in the advanced genome editing space, to exemplify how light can be shed onto
complicated patent landscapes with different stakeholders (J Biotechnol, Oct 2025).



Dr. Jason Bock describes the risks and critical considerations therapy developers must confront as they advance their programs, and shares meaningful insights for building a strategy for successfully navigating and overcoming these challenges. Read the article on how a strategic, collaborative approach can accelerate product development and bring cell therapies to patients (CGT Review, Sep 2025).

A multidimensional analysis on longitudinal tumor and blood samples in a clinical trial of TIL therapy in 16 patients with metastatic NSCLC showed that **tumor neoantigen-reactive clonotypes** were less cytolytic, expressed a dysfunctional program, and lacked stem/memory-like self-renewal in patients that did not clinically benefit. Further, loss of infused cells or of neoantigen-reactive peripheral T cell clonotypes over time was associated with the onset of progressive disease. Subclonal neoantigens that were previously targeted by infused TILs were absent from tumor cell genomes upon progression, suggesting adaptive resistance (Nature Cancer, May 2025).



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 May 2025
EMA/CAT/174611/2025
Human Medicines Division

CAT quarterly highlights and approved ATMPs

May 2025

Quarterly highlights and approved ATMPs by the Committee for Advanced Therapies

ATMP LANDSCAPE: WHAT HAPPENS IN THE NETWORK

EATRIS, the European infrastructure for translational medicine, as part of the EU-funded PRECISEU project, has developed an ATMP survey aimed at creating a capacity map for ATMP activities across the EU. This initiative builds on the ATMP Sweden model, featuring an interactive map, expanding the scope through working closely with the EMA, who will use the resulting map as their point of reference. This strategic initiative is designed to strengthen Europe's preparedness and infrastructure for delivering cutting-edge therapies, ensuring that patients across all regions have equitable access to life-saving innovations in ATMPs. Read more about it here and fill in the survey to add your facility to the map - it should take no longer than 10-15 mins max.
Keeping this map updated with all stakeholders (including academia and industry) will be a priority for EATRIS the coming years. DARE-NL is discussing with EATRIS, FAST, JOIN4ATMP and others how to optimally use the data collected from different surveys on this topic.

The Accelerating Clinical Trials in the EU (ACT EU) initiative launched a survey earlier this year to capture the **clinical trials training needs** of academia and micro, small and medium-sized enterprises (SMEs) involved in the research and/or development of medicines for human use. A report on the analysis of ~400 entries has now been published. The inventory of clinical trial training needs of academia and SMEs also highlights potential gaps in clinical trials training and lists ways to address them. The most frequently reported challenge for stakeholders is finding relevant trainings. To address this, ACT EU will map and signpost the most important clinical trials trainings (EMA, Jul 2025).

The second edition of the EU CAR-T Handbook covering the latest developments in CAR-T cell therapies was launched. The handbook is a collaboration between EBMT, EHA and GoCART and its updated edition provides expanded insights into scientific advances, clinical applications, and evolving regulatory frameworks. This edition contains a section on DARE-NL in chapter 21: National Network to Support ATMPs Development and Evaluation. Edwin Bremer and Emma de Pater also authored chapters in the handbook.

The European Medicines Agency (EMA) has updated its Academia webpage with the latest overview of available support offerings and engagement pathways for academic and not-for-profit researchers working on medicine development and regulatory science. New additions include:

- Reduced fees for scientific advice starting 1 January 2025, under the new fee regulation, making regulatory support more accessible to entities not engaged in economic activities;
- A clearer overview of tailored support offerings for academic and not-for-profit developers;
- Fresh insights into how EMA collaborates with academia to advance medicine development, regulatory evaluation and deliver regulatory science solutions.

GoCART launched a pilot program to support trainees from emerging CART centers to conduct a 1 to 2-week placement with established CART centres to learn best practices for developing a successful cellular therapy programme. The pilot program will focus on centers in Europe and GoCART expects to expand to other regions in 2026. Applications from emerging centers in Europe have been invited to nominate a trainee and from established centres in Europe to host the trainee (deadline 15 September).

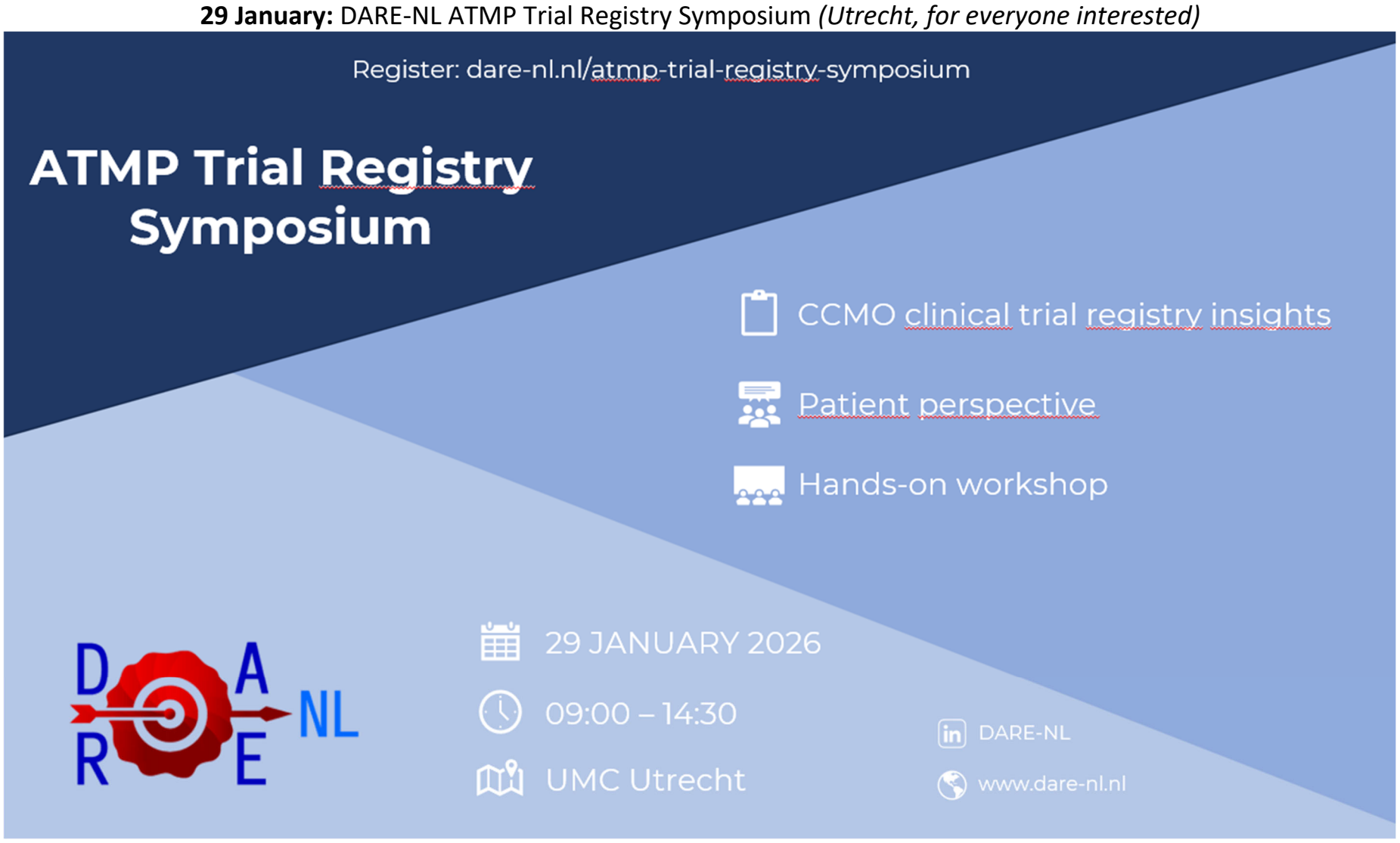
DARE-NL steering committee members Trudy Straetemans and Lourens Bloem are involved as steering committee member of the organization to setup **ATMP-NL**, a national network for ATMPs for all stakeholders, securing a close connection with DARE-NL. Find an update (in Dutch) on the FAST website. In short, a widely supported model that structurally facilitates collaboration, knowledge sharing and support within the field is developed based on analyses and various meetings with stakeholders. The goal is to develop a sustainable concept and implementation plan for ATMP-NL, actively building on existing knowledge and initiatives. Co-creation with the field is central to ensuring a broadly supported and feasible approach. Several activities are planned for the coming period to achieve this.

Renske ten Ham explained in the AD why medications are sometimes so expensive, and who decides whether they are reimbursed (in Dutch).

CALENDAR

See website (public) & SharePoint (members only)

30 October: DARE-NL workshop ATMP trials & the CCMO: common challenges and shared insights *(Rotterdam, for members)*
29 January: DARE-NL ATMP Trial Registry Symposium *(Utrecht, for everyone interested)*



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