

Annual Report 2022

(YEAR 3)











PROJECT TITLE:

Empowering families through technology: a mobile-health project to reduce the TAND identification and treatment gap (TAND^{em})

FUNDER:

Fund Dr & Mrs Charles Tournay-Dubuisson, managed by the King Baudouin Foundation

AGREEMENT NUMBER:

2019-J1120010-213544

PRINCIPAL INVESTIGATOR:

Prof. Petrus J de Vries, University of Cape Town, South Africa

CO-PI:

Prof. Anna Jansen, Vrije Universiteit Brussel, Belgium

GRANT PERIOD:

4 years

STARTING DATE OF THE PROJECT:

1 November 2019





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Welcome from the TANDem PI and co-PI

Welcome to the report on year 3 of the TAND^{em} project, generously supported by the King Baudouin Foundation in Belgium. In this report we will present key milestones over the last year and highlight some important and exciting activities and achievements by the TAND^{em} team during this period.

First a note on the cover of this year's annual report. It was exactly 10 years ago, in 2012, that the term 'TAND' (TSC-Associated Neuropsychiatric Disorders) was coined at an international consensus conference in the USA. Various clinical researchers represented today in the TAND Consortium were part of that milestone in the history of TSC research. We have been delighted by the way in which the TSC community (and particularly families) have embraced the umbrella term coined by us. It therefore felt appropriate to have a big celebratory TAND cake on the front cover of this issue!

The TAND^{em} project has an inextricable link with the COVID-19 pandemic which clearly influenced some of the ways we have conducted the study. In year 1 we were able to have an in-person launch for the project in Leuven, Belgium. This laid a solid participatory foundation for the goals and collaborative spirit of the TAND Consortium and project goals. The whole of year 2 was conducted virtually as a result of the pandemic. However, in spite of this challenge, Zoom became our best friend, and the TAND Consortium was able to develop a draft of the TAND-SQ Checklist, progress well on the app development, conduct a consensus conference, draft consensus recommendation chapters, and participate in a wide range of (online) impact activities.

Year 3 of the TAND^{em} project was a transitional year from the virtual world of communication and research back to in-person engagement and activities. After almost two years of not seeing TAND Consortium members, we were able to start connecting with one another again. A highlight of this transition was the participation of various TAND Consortium members in the TSC Alliance World Conference which took place in Dallas, Texas in July 2022.



The TAND^{em} project was very well represented in the Opening Session as well as in many other lectures, workshops and discussions. We also took the opportunity to have an in-person engagement with the Tuberous Sclerosis International (TSCi) community to start thinking about next steps after the completion of the TAND^{em} project in October 2023.

We hope that you will enjoy reading about the project and its development. In particular, we hope you will see how we have been able to turn challenges posed by COVID-19, regulatory delays and other life events into opportunities for creative solutions in keeping with the spirit and aims of the TAND^{em} project.



Prof. Petrus J de Vries and Prof. Anna Jansen

ties

Prof. Petrus J de Vries
MBChB, FRCPsych, PhD
PI (University of Cape Town)

Prof. Anna Jansen
MD, PhD
co-PI (Vrije Universiteit Brussel)



The TANDem project in a nutshell



Tuberous Sclerosis Complex (TSC) is a rare genetic disorder that affects about 1–2 million people around the globe. People with TSC have a wide range of physical manifestations including growths in many organs of the body, including the brain. **TSC-A**ssociated **N**europsychiatric **D**isorders (**TAND**) represent the number one concern to families around the globe, yet they are highly under-identified and under-treated – we refer to these as an 'identification gap' and a 'treatment gap' [1, 2].

Project background

In 2012 we introduced the term 'TAND' and in 2015 created the TAND Checklist to reduce the 'identification gap' [3]. Research using the TAND Checklist showed that we could identify seven natural TAND Clusters that may be useful to reduce both the identification and treatment gaps for TAND further [4,5]. Following our earlier work, community-based participatory research with families and a range of TSC stakeholders identified three next steps for action:

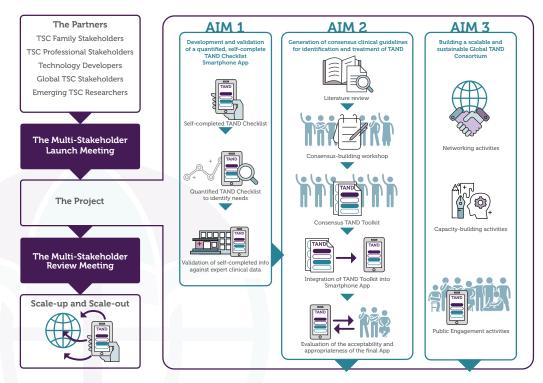
- 1 Creation of a self-report and quantified version of the TAND Checklist
- 2 Creation of a digital tool such as an app for the TAND Checklist
- 3 Generation of evidence-based guidelines and a toolkit for next-step management of TAND Clusters

TANDem project aims

The TAND^{em} project was a direct result of the feedback from our TSC stakeholders, and has three aims:

- AIM 1: Development and validation of a quantified, self-report TAND Checklist (TAND-SQ), built as a mobile app
- AIM 2: Generation of consensus clinical guidelines for identification and treatment of TAND Clusters, to be incorporated as a toolkit into the app
- AIM 3: Establishment of a global TAND consortium through a range of networking, capacity-building and public engagement activities

More details on the project can be found in our recently published protocol paper^[1].



References:

- [1] Heunis et al., (2022) Frontiers in Psychiatry, 13: 834628
- [2] King Baudouin Foundation (2018) Mind the Gap! Working together to set research priorities for Tuberous Sclerosis Complex. Pub No 3555
- [3] de Vries et al., (2015) Pediatric Neurology, 52: 25-35
- [4] Leclezio et al., (2018) Pediatric Neurology, 81: 38-44
- [5] de Vries et al., (2020) Journal of Neurodevelopmental Disorders, 12: 24

Year 3 – transitioning from the virtual world back into the real world

At the end of year 2 we agreed on 12 next steps for the TAND^{em} project.

The goals were:

- a Complete pre-piloting of the paper version of the TAND-SQ
- Publish the TAND-SQ in the peer-reviewed literature and make it available through the TAND Consortium website
- c Complete phase I app development
- d Collect TAND-SQ data via the app and via the TSC Alliance portal
- e Complete evaluation of the technical feasibility of the app
- f Complete validation of TAND-SQ data in relation to expert data (Boston/Cincinnati) and real-life clinical data (TSC Alliance)

- g Complete development and design of the TAND Toolkit materials
- h Incorporate the toolkit into the app (phase II of app development)
- i Perform evaluation of the feasibility of the complete TAND Toolkit app (Belgium, USA)
- j Publish a range of peer-reviewed articles related to the project
- k Participate in the 2022 TSC World Conference (USA), including TAND^{em} activities with the TSC community
- Participate in other dissemination activities

This report outlines achievements in relation to these goals in year 3 of the TAND^{em} project, and represents the formal report as stipulated in the specific conditions of the grant.



Towards a final TAND-SQ Checklist

In year 2 we developed, designed and prepiloted the self-report, quantified version of the TAND Checklist (referred to as the TAND-SQ Checklist). The beautifully designed TAND-SQ Checklist was then used for formal feasibility evaluation by members of the TAND Consortium and by TSC families from the USA who completed the TAND-SQ Checklist through the TSC Alliance portal. More than 50 participants provided feedback on various aspects of the TAND-SQ Checklist including comprehensiveness, clarity, presentation, and were asked to suggest additions or changes.

Family and professional participants gave the TAND-SQ Checklist high ratings for ease of use, comprehensiveness, clarity and presentation, and gave high overall ratings of the new checklist.

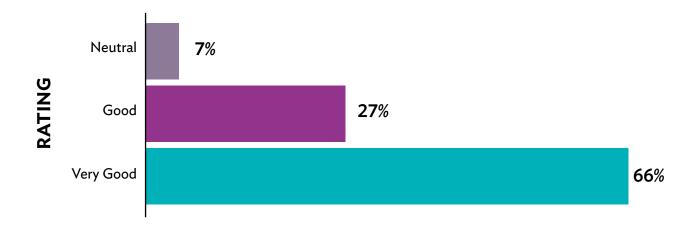
Participants also gave very helpful feedback on ways to improve the TAND-SQ Checklist. One of the surprising (but important) suggestions was the need not only to ask about difficulties and challenges, but also to document strengths and



talents in individuals with TSC. In addition, a guide to calculate TAND clusters was suggested. These recommendations were therefore added to the final TAND-SQ Checklist.

A peer-reviewed article on the development of the TAND-SQ Checklist, its feasibility evaluation, and a final version of the TAND-SQ Checklist, is currently in preparation. We hope that this will be published early in year 4 of the TAND^{em} project.

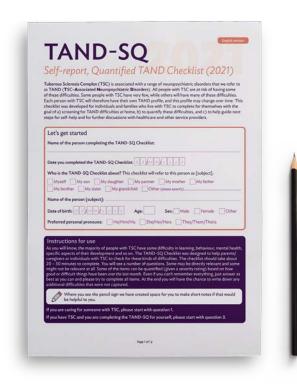
What is your overall rating of the TAND-SQ checklist?



The TSC Alliance portal for TAND-SQ data collection

A very positive initiative in year 3 was development of an electronic portal for completion of the TAND-SQ Checklist through the TSC Alliance Natural History Database. The Natural History Database was set up by the TSC Alliance to collect natural history data on all aspects of TSC. After discussions between the TSC Alliance and the TANDem team, we agreed to build the TAND-SQ Checklist into the database a) to perform feasibility evaluation and validation of the TAND-SQ Checklist, and b) to then have the TAND-SQ Checklist available as a data collection tool for all participants in the Natural History Database. In the context of the TANDem project, we aim to include at least 100 participants in this part of the project.

We are very grateful for the support from Kari Rosbeck (President & CEO of the TSC Alliance), Steve Roberds (Chief Scientific Officer of the TSC Alliance), Jo Anne Nakagawa (Director of Clinical Projects at the TSC Alliance) and John Pudzke (Studytrax). A particular thanks to Gabrielle Rushing (Director of Research at the TSC Alliance) for coordinating discussions and actions.





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A final app for data collection

After many iterations and preparatory steps in the design and building of the TAND Toolkit app, internal testing was performed by all members of the TAND Consortium. Members were asked to complete the TSC Story and TAND-SQ Checklist on paper, then to download the app onto an iOS or Android device, and then to complete the TSC Story and TAND-SQ Checklist on the app. They were asked to compare their input data captured on paper with the summary TSC Story and TAND-SQ Checklist PDF outputs generated by the app, in order to check that data were captured and reported accurately. They were also asked to complete an app feedback form as part of a survey on the app. Data from these feedback forms were collated and reviewed by the Technology Group, Family Representatives Group, and Action Group in order to plan essential revisions to the app. Following these app revisions, a final app was prepared by our technology

partner. After approval of the final app by the Action Group, the app was uploaded onto GDPR compliant Amazon web servers, ready for data collection in the USA.

Tosca Heunis, our project coordinator, drew an 'app data flow diagram' to show how app data would move between different sites, and indicating the roles and responsibilities of all parties involved with app data collection in the TAND^{em} project. Boston Children's Hospital and Cincinnati Children's Hospital are the data providers, responsible for recruiting and enrolling participants and getting them to complete the TAND Toolkit app. The TAND^{em} team is responsible for collection and secure storage of data, merging clinical and app data, data quality control and analysis. Our technology partner provides app and backend feature development, and additional support upon request.



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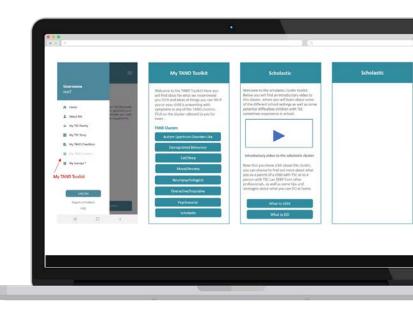
TAND Toolkit materials ready for the app

In year 2 the TAND Consortium performed detailed literature reviews based on clusters, and developed the consensus recommendations for identification and treatment of TAND. Linked to these two actions, the consortium also agreed on the kind of information to include in the TAND Toolkit. Year 3 therefore included a series of 'creative sessions' to convert the evidence-based and evidence-informed data collected into short, usable and practical 'app screens' that could be incorporated into the app. Cluster leads and their teams took turns to present their ideas and designs to the wider team. We acknowledged that each cluster may have unique content, but wanted to make sure that there would be some standardisation of presentation to make navigation of the TAND Toolkit as easy as possible for families.

The TAND Toolkit draft will include a short introductory movie about each specific cluster, a section on 'what to seek' (including which types of evaluations or specialists to approach for clarification of challenges in that specific cluster), as well as a section on 'what to do' (with tips, information and self-help guidance for families to implement immediately).

At the time of this report, the Action Group was exploring the most suitable technological solution to embed the toolkit content into the TAND Toolkit app, whilst maintaining the ability to make future content updates easily and flexibly. Once all toolkit elements have been linked to the app, feasibility evaluation of the whole TAND Toolkit app will be performed in Belgium and in the USA.





TANDem publications

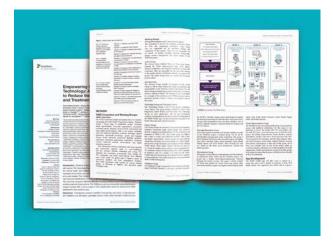
We were delighted that two peer-reviewed articles were published in year 3 of the TAND^{em} project. The first was the publication of a comprehensive scoping review on all TAND research that had ever been published until 2020. This milestone publication, led by two of our early career researchers (Stephanie Vanclooster and Stacey Bissell) was accepted in the Journal of Neurodevelopmental Disorders, and is likely to become a landmark paper in the story about TAND. At the time of this report, the article had been accessed more than 2,500 times since publication in February 2022.

The second TAND Consortium publication was a comprehensive paper that outlined the protocol of the TAND^{em} project, led by Tosca Heunis. This mammoth article outlined all aspects of the background, methodology and key technology considerations for the TAND^{em} project. The paper, published in Frontiers in Psychiatry, also in February 2022, had been accessed more than 2,000 times at the time of this report, and provides an excellent protocol template for other rare disease and neurodevelopmental research teams.



The next two priority papers for the TAND Consortium are the publication of the TAND-SQ Checklist, and the finalisation and submission of the consensus recommendations for identification and treatment of TAND. Both these are in progress.





The TAND Mini-Symposium 2022

Aim 3 of the TAND^{em} project is to provide networking opportunities around TAND research and to inspire the next generation of TAND researchers through research capacity-building activities. The TAND Consortium therefore decided to host an online 'mini-symposium' in April 2022. Emerging and established TAND researchers across the globe were invited to submit abstracts for short 'rapid fire' presentations on their research.

Excellent format and short presentations wonderful as they give an overview of several angles.

After a brief welcome, setting the scene and summary of the story of TAND and TANDem by Petrus de Vries, Anna Jansen, Eva Schoeters, Stephanie Vanclooster and Stacey Bissell, ten researchers from 6 countries (UK, USA, South Africa, Brazil, India, The Netherlands) presented research on a wide range of topics ranging from preclinical to clinical and intervention/qualitative research. The highly interdisciplinary and international group of ~60 attendees participated in a stimulating set of discussions. Feedback from participants was very positive and they strongly encouraged the TAND Consortium to arrange similar mini-symposia in future.

Yes, an annual meeting would be great.





2022 TAND^{em} Seed Grants in association with the Tuberous Sclerosis Association, UK

The TANDem project was co-funded by the Tuberous Sclerosis Association in the UK. Funding from the TSA UK was directed to support the technology component and to fund a TAND Consortium meeting in year 2 of the project, to be coordinated with the international TSC Conference planned as an in-person meeting in London. The COVID-19 pandemic and international travel restrictions forced the TSC conference as well as the TAND Consortium meeting to be done as virtual meetings. At one of the TAND Consortium meetings, a highly creative suggestion was made to seek permission from the TSA UK to convert the consortium meeting budget into 'seed funding' for a number of small TAND grants that could bolt onto the broader TANDem project. After consultation, review, and approval by the TSA UK Board, the TAND Consortium and TSA UK released a grant call for 'TAND^{em} seed grants'. The TSA UK research team very generously agreed to administer the process.

A total of seven grant applications were submitted from six countries. After review, the panel made three awards to researchers representing three countries on three different continents! Projects will start by 1 October 2022 and will have a duration of one year. Details of the three seed grants will be presented in the year 4 TAND^{em} report.

We are extremely grateful to the TSA UK and in particular to Louise Fisch (Chief Executive), Pooja Takhar (Head of Research and Policy) and Bethan Vaughan (Research and Policy Manager) for their outstanding support.





Hello and goodbye to TANDem team members

Year 3 saw some changes in the TAND^{em} team.

After two-and-a-half years working as post-doctoral researcher on the TAND^{em} project, Stephanie Vanclooster accepted a post to train as a genetic councillor at the Antwerp University Hospital in Belgium. We were very grateful for all her work on the project over the years, and wish Stephanie all the best for her new career. We hope that her career decision was, at least in part, inspired by her work in the TSC community!

In order to fill the staff gap, we were delighted to appoint an existing TAND Consortium member, Nola Chambers, to join the project more formally as senior research associate, with her base at the University of Cape Town in South Africa.

Nola is a speech & language therapist and did her undergraduate and master's training at the University of the Witwatersrand (WITS) in Johannesburg, South Africa. She worked in various clinical settings in South Africa and the UK before becoming a lecturer and then senior lecturer at WITS. She later moved to the USA where she completed a PhD at Florida State University with Prof Amy M Wetherby on early detection and early intervention for autism. Apart from her work in the TAND consortium, Nola's current research uses a community-based implementation science approach to the implementation of evidencebased parent/caregiver education and parent/ caregiver-mediated interventions for children with autism.



Stephanie Vanclooster



Nola Chambers

Global dissemination activities

A broad range of impact and dissemination activities were implemented by the TAND Consortium in year 3, not only virtually but also in person. These activities included:

- Child Neurology Society Annual Meeting, 29 Sept 2 Oct 2021, Boston (USA)
- Stichting Tubereuze Sklerosis Nederland (STSN) Lustrum Symposium, 6 Nov 2021, Ede (The Netherlands)
- European Paediatric Neurology Society (EPNS) Congress, 28 Apr-2 May 2021, Glasgow (Scotland)
- World TSC Conference, 28–31 Jul 2022, Dallas (USA)
- SSBP International Research Symposium, 8–10 Sept 2022, Oslo (Norway)
- Tuberous Sclerosis Australia, 20 Nov 2021, Sydney (Australia) and online
- Danish TSC Association, 17 Sept 2022, Copenhagen (Denmark) and online
- Online seminar in association with Pretola, a non-profit organisation providing training in low- and middle-income countries, mainly in *Africa*, 12 Feb 2022
- Social media activities on Twitter (@TANDconsortium) and Instagram (tandconsortium)nstagram (tandconsortium)





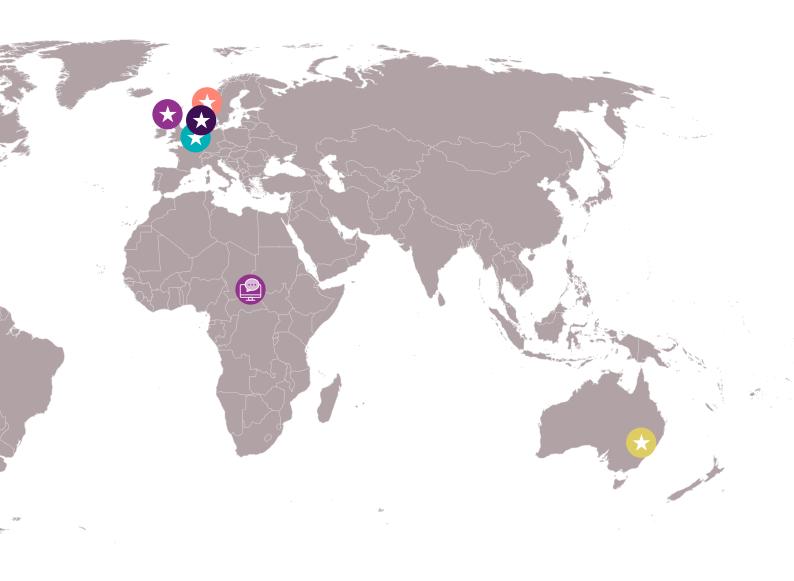
SSBP International Research Symposium, 8--10 Sept 2022, Oslo (Norway)

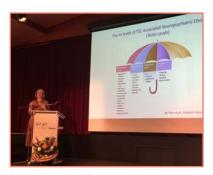


SSBP International Research Symposium, 8-10 Sept 2022 2022, Oslo (Norway)



And off we go... TANDem team off to another event





STSN Lustrum Symposium, 6 Nov 2021, Ede (The Netherlands)



Danish TSA screenshot



TAND Mini-symposium screenshot

Awards to the TAND^{em} team

Over the last year TAND Consortium members received three awards for work directly or indirectly related to the TAND^{em} project.

The STSN Bourneville Prize

Petrus de Vries (PI) was awarded the Bourneville Prize by the Dutch TSC Association, Stichting Tubereuze Sclerosis Nederland (STSN), for his work on TAND. The award, made every five years by the STSN, was presented at the 6th STSN Lustrum that took place in the Netherlands in November 2021. The prize included a certificate, a bronze medal and a cash prize to be used towards research. The prize was named after Bourneville, the 19th century neurologist who first described TSC at the Salpêtrière Hospital in Paris.

The inscription on the award read: "For his unique gift to explain the complex problems of TSC in an inspiring way to parents and patients as well as to scientists. For his involvement in, drawing attention to and contribution to research into neuropsychiatric problems in TSC (TAND)". Previous award winners included Dr Manuel Gomez (often referred to as 'the father of TSC research') and the Rotterdam TSC Team who led



Petrus de Vries with TAND Consortium members Liesbeth De Waele, Tosca Heunis, Anna Jansen, Eva Schoeters and Stephanie Vanclooster



Prof de Vries with the Chairman of STSN

Surprise to receive the 2021
Bourneville Prize! For those who know me, I am not often left completely speechless. Needless to say, an award like this is not really to an individual, but actually an acknowledgement of the work of many people over a long period of time. So, thank you to everyone who contributed to our TAND research and who inspired me over the years



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From Left to right: Anna Jansen, Agnies van Eeghen, Stacey Bissell, Pat Howlin (SSBP President), Honey Heussler (SSBP Chairman) and Petrus de Vries

discovery of the TSC1 gene. After receiving the award, Petrus de Vries said: "It was a complete, but wonderful surprise to receive the 2021 Bourneville Prize! For those who know me, I am not often left completely speechless. Needless to say, an award like this is not really to an individual, but actually an acknowledgement of the work of many people over a long period of time. So, thank you to everyone who contributed to our TAND research and who inspired me over the years."

Two prizes at the SSBP International Research Consortium

At the 24th International Research Symposium of the Society for the Study of Behavioural Phenotypes (SSBP), the TAND Consortium was awarded two prizes for the TAND^{em} project. The first was the Pat Howlin Prize Lecture, an award to a junior member of the SSBP for intervention-based research that links directly to the learning and behavioural problems of people with genetic syndromes and related neurodevelopmental disorders. The second award was the Leclezio-de Vries Lecture, made to a junior member of the SSBP for socially responsive research with a particular emphasis on community participation. The TAND Consortium were delighted to have been selected to receive both awards.



Bourneville Medal

The TSC Alliance 2022 World Conference

The TSC Alliance, the main US-based nonprofit organisation for TSC, organises a 'world conference' for families and people who live with TSC from all over the globe every 4 years. The 6th World Conference took place in Dallas, Texas, in July 2022, and the TAND Consortium were very well represented at the meeting. Petrus de Vries and Eva Schoeters were invited to be speakers in the Opening Session of the meeting, attended virtually or in person by more than 900 families from 31 countries. Various other TAND Consortium members including Mustafa Sahin, Darcy Krueger, Tanjala Gipson, Chris Kingswood, and Anna Jansen led lectures, workshops and discussions or acted as moderators. Anna also acted as moderator of the Closing Session. Peter Davis and Jennifer Flinn were both scheduled to join the speaker list, but were unable to attend due to other commitments.

The TAND^{em} team decided to have a table in the exhibition hall. Tosca Heunis and Katie Smith prepared a wonderful poster and printed materials for participants. We also designed and printed a TAND^{em} 'lapel pin' to share with families.

On the day prior to the World Conference, representatives from Tuberous Sclerosis International (TSCi) held a half-day workshop to review and plan global TSC activities. The meeting was attended by participants from a wide range of countries including the UK, USA, Canada, Ireland, Germany, Denmark, Italy, India, Portugal, Israel, Brazil, Hungary, South Africa, and Serbia. Petrus and Anna led a discussion with TSCi representatives on the TAND^{em} project with a particular emphasis on next steps after completion of the TANDem project. This provided invaluable feedback and suggestions from the global TSC community that will inform our discussions at the TAND Consortium review meeting scheduled for November 2022 in South Africa.



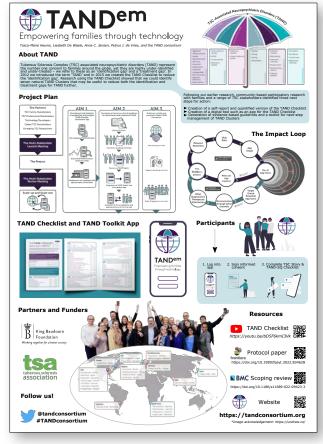
National Representatives from TSCi



An presenting TAND em project to TSCi, 28 July 2022, Dallas (USA)



TAND team members together in Dallas



TANDem Dallas poster



TANDem table in Dallas



Travelling TANDem team



An and Petrus at the TANDem table in Dallas



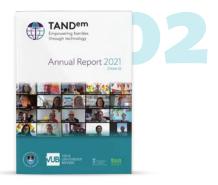
Petrus and Tanjala with fellow speakers

12 Next steps for year 4

Over the next 12 months (year 4 of the project) we will need to complete all key aims of the TAND^{em} project. These include:

- a Publication of the TAND-SQ Checklist
- b Publication of consensus recommendations for the identification and treatment of TAND
- Data collection and validation of the TAND-SQ Checklist against expert and real-world clinical data
- d Embedding the TAND toolkit into the app and feasibility evaluation of the overall TAND Toolkit app
- Preparation of publications related to TAND-SQ Checklist validation and app feasibility
- f Further networking and impact activities, including support to the 'seed funded' grants
- g Reviewing the TAND^{em} project and planning of next steps for scale-up and scale-out of the TAND Toolkit app
- h Writing a final report to the King Baudouin Foundation













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