



## Original Article

# Beyond the Guidelines: How We Can Improve Healthcare for People With Tuberous Sclerosis Complex Around the World



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## ABSTRACT

**Background:** Tuberous Sclerosis Complex International (TSCi) is a consortium of organizations that supports individuals with tuberous sclerosis complex (TSC) around the world. To improve care for TSC on a global level, TSCi identified the need to expand understanding about existing resources available in other countries, what individuals and caregivers value in TSC care, key gaps between needs and reality in each country, and ways these gaps can be addressed by advocacy organizations around the world.

**Methods:** An iterative, mixed methods approach (the Improving Care project) was adopted to incorporate views from diverse members of TSCi. Through idea generation, a collection of qualitative open-ended responses and concept elicitation, we were able to build consensus where shared experiences and opinions were identified.

**Results:** The research performed as a part of the Improving Care project revealed a significant gap between the guidelines and what is actually available to people with TSC worldwide. Three key priority areas of action to improve this gap were identified: (1) implementation of the guidelines; (2) access to TSC expertise, and (3) coordinated and integrated health care.

**Conclusions:** There are significant opportunities for key stakeholders, including organizations, clinicians, and researchers to improve care for individuals with TSC on both local and global levels. Working across stakeholder groups and utilizing TSC organizations are essential to ensure that the advances in TSC research benefit people living with TSC around the world.

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## Introduction

Tuberous sclerosis complex (TSC) is a genetic disorder affecting over one million people around the world.<sup>1</sup> TSC is characterized by a variety of manifestations including nonmalignant tumors in the brain, kidneys, heart, lungs, and skin; epilepsy; pulmonary and renal complications; and a range of TSC-associated neuropsychiatric disorders (TANDs), including intellectual disability (ID) and autism spectrum disorder.<sup>2</sup> TSC is a complex condition that can be difficult for both affected individuals and their caregivers to manage.<sup>3</sup> It often requires substantial utilization of health care resources.<sup>4,5</sup> Research in the last 20 years has made incredible discoveries and resulted in new therapies for people with TSC.<sup>6,7</sup> In 2012 the International Tuberous Sclerosis Consensus Conference published updated diagnostic criteria<sup>1</sup> and revised recommendations for surveillance and management that define optimal clinical care for people with TSC.<sup>2</sup> Diagnostic Criteria and Surveillance and Management Recommendations have been recently updated in 2021 to incorporate new evidence and understanding of TSC pathogenesis and clinical treatment as well as to address unintended ambiguity or obstacles discovered since 2012 that hindered guidelines adoption and practices (H. Northrup et al., unpublished data, 2021).

Tuberous Sclerosis Complex International (TSCi) is a worldwide association of TSC organizations, with each member organization undertaking a combination of information, support, research, and systemic advocacy in their own countries.<sup>8</sup> In 2015 TSCi began the Improving Care project to identify ways to improve the health care available to people with TSC.

The project aimed to

- understand what individuals with TSC and their caregivers value in TSC care;
- understand the care available to people with TSC around the world;
- identify key gaps in care around the world;
- identify initiatives to bridge the gap in care;
- identify key research questions to be explored in the future.

Research from the Improving Care project suggests that this standard of care is only available to a small proportion of people with TSC. We also recognize that ideal health care for people with TSC goes beyond a checklist of tests and treatments. TSCi and its member organizations present this paper as a shared strategy for the global TSC community.

The project focused on health care for people already diagnosed with TSC. The project did not focus on issues relating to receiving a diagnosis of TSC or on the education and disability supports that a person with TSC may need.

The project included surveys, interviews, and workshops with volunteer TSC advocates from TSCi member organizations,<sup>8</sup> interviews and discussions with medical specialists who care for patients with TSC, and a global survey of patients with TSC and their family members. These activities were conducted between 2015 and 2017 (Fig 1).

The community of people with TSC is diverse. Different people with TSC will have different signs and symptoms of TSC developing at different ages and with different severities. TSC has a similar incidence throughout the world, meaning that people with TSC live in countries with differently resourced health systems and individuals with TSC have different levels of access to public and private health care. Current TSCi membership overrepresents high-income and developed countries and underrepresents middle- and low-income and developing countries, so the issues identified are

possibly biased toward higher-income settings. We have little or no access to data from developing countries.

Even though this diversity and complexity is a challenge, there is ample opportunity to improve care. This project has uncovered several areas for action that have the potential to improve the health care for many of the one million people living with TSC around the world. We identified the following three priorities:

1. Health care that implements the guidelines.
2. Health care that has access to TSC expertise.
3. Health care that is coordinated and integrated.

We believe that together we can ensure that the discoveries made by TSC research improve the lives of as many people as possible who live with TSC, while we continue to work toward a cure for the future.

### Priority 1: People with TSC need health care that implements the clinical guidelines

The outcome of the 2012 International Consensus Conference for TSC was the publication of updated guidelines for the diagnosis, surveillance, and management of TSC.<sup>1,2</sup> These guidelines represent the ideal standard of care for people affected with TSC. These clinical guidelines are valuable to TSCi member organizations because they provide a consistent starting point for health professionals around the world to provide optimal clinical care for their patients with TSC.

The research done as a part of the Improving Care project revealed a significant gap between the 2012 guidelines and what is actually available to people with TSC. We identified the following three key areas of action to improve this:

- Awareness and knowledge of the guidelines
- Access to imaging
- Access to treatments

#### Awareness and knowledge of the guidelines

Awareness of the guidelines amongst people with TSC, caregivers, and health professionals is an important first step to implementing them. The guidelines were published as open access articles, and many TSC organizations have promoted the guidelines within their own countries. Patient advocates from around the world report that people with TSC and/or their caregivers will bring the guidelines to the attention of their clinicians and use them as a tool to advocate for the clinical care they describe. However, the project found low rates of knowledge of the guidelines among the wider TSC population. Thanks to work done by the local association, Portugal is the only country that has adapted the *Diagnóstico e Seguimento da Pessoa com Esclerose Tuberosa em Idade Pediátrica e no Adulto* into their health system.<sup>9</sup> The Ministry of Health in Portugal accepted these guidelines in 2018.<sup>9</sup>

The project's 2017 International Drug Development survey for individuals with TSC and caregivers asked respondents from 54 countries whether they had read the guidelines.<sup>10</sup> Survey questions were translated and available in English, Spanish, and French. Although nonrepresentative of all countries, the results of this survey suggest that knowledge of the guidelines among people with TSC and caregivers may be low (30%) and there is high variation between countries. For nations with five or more respondents to this question, results ranged between no knowledge (Costa Rica) and 80% (Sweden), with a median of 29% of respondents being

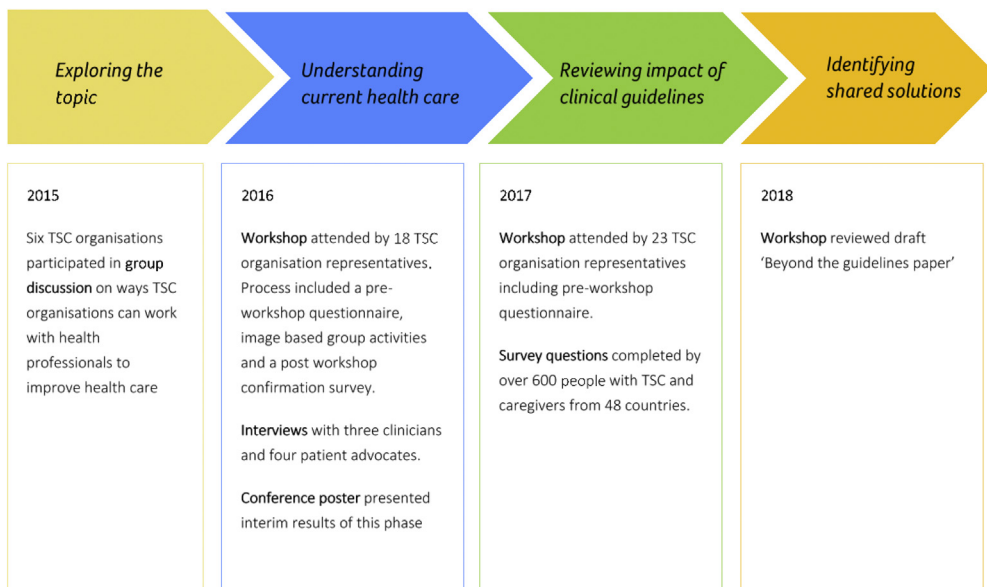


FIGURE 1. Stages of the Tuberous Sclerosis Complex International's improving care project. The color version of this figure is available in the online edition.

aware of the guidelines (Netherlands) (Fig 2). The survey also asked if respondents had shared the guidelines with their doctors. Overall, only 48% of respondents had done this. For countries with five or more respondents to this question, results ranged between 14% (France) and 100% (Peru and Colombia), with a median of 37% (Germany) (Fig 3). The survey was limited in that not all countries were represented and questions were not available in all languages.

In addition to this survey, a study of patients with TSC and their parents in France and Norway found similar variation in knowledge of kidney manifestations of TSC and recommended surveillance.<sup>11</sup>

Further work could be done with patients with TSC and their caregivers to monitor awareness of the guidelines and identify effective ways of increasing knowledge of them.

The 2017 survey did not include work to understand how aware health professionals are of the guidelines. Although it would not be practical to ask every health professional to know about the guidelines, it may be possible to identify key subgroups such as neurologists who are most likely to play a significant role in the care of people with TSC.

#### Access to imaging

Even when people with TSC and caregivers are aware of the guidelines, they still face barriers to receiving the recommended surveillance and treatments. Based on the surveys, patient

### Patients and caregivers who have read TSC clinical guidelines

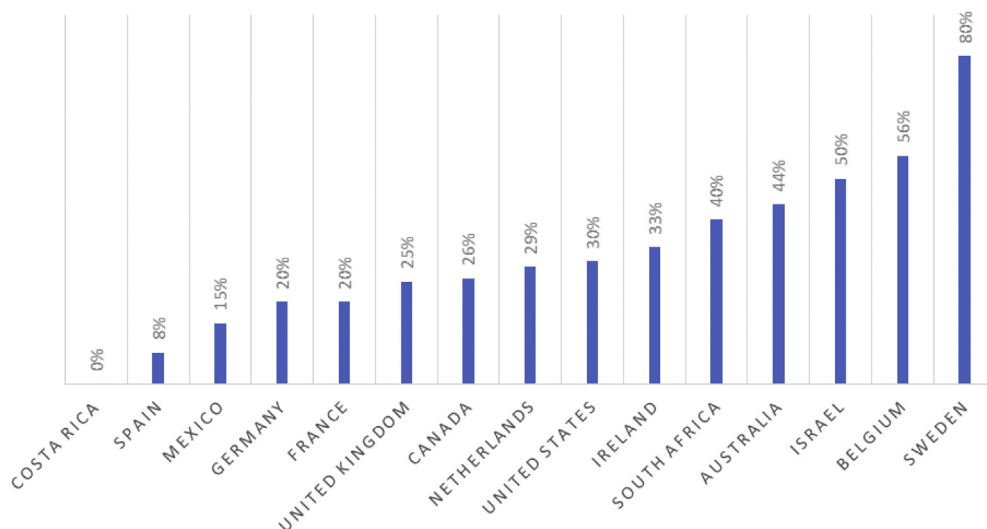


FIGURE 2. 2017 International Drug Development survey response to patient and caregiver familiarity with the guidelines (countries with five or more respondents). The color version of this figure is available in the online edition.

advocates identified access to imaging as a significant challenge to implementation of the clinical guidelines in their regions.

The guidelines recommend baseline and surveillance brain and abdominal magnetic resonance imaging (MRI).<sup>2</sup> Although computed tomographic (CT) scans and ultrasound can be accepted as substitutes when MRI is not available, they have limitations. Concept elicitation from TSCi member organizations identified widespread challenges in accessing the recommended imaging, especially

- ultrasound and CT scans being used in place of MRIs for monitoring of kidney angiomyolipomas, further explored in the United States by Swallow et al.<sup>12</sup>;
- CT scans being used in place of MRIs for surveillance for subependymal giant cell astrocytoma;
- clinicians' hesitance to image under sedation for children and people with ID.

### Access to treatments

The guidelines include several recommended treatments for the various signs and symptoms of TSC, but many of these are not available to vast numbers of people with TSC throughout the world.

Mammalian target of rapamycin (mTOR) inhibitor treatment of subependymal giant cell astrocytoma, kidney angiomyolipomas, lymphangioleiomyomatosis, and epilepsy in TSC is now approved by regulators in many parts of the world, but not all.<sup>13-16</sup> In addition, funding for the medicine is not straightforward, with many patients lacking access to affordable mTOR inhibitors, depending on each country's health care system. Moreover, topical mTOR inhibitors have been included in the guidelines as recommended treatment for facial angiofibromas but have only been approved in Japan thus far<sup>17</sup> and are available in other countries as part of research studies only per [ClinicalTrials.gov](http://ClinicalTrials.gov).<sup>18</sup> Vigabatrin is the recommended first-line treatment for infantile spasms in infants younger than two years with TSC.<sup>2</sup> However, these treatment options are not accessible to everyone around the world.

With most patents on these medicines expired or soon expiring, there is a declining commercial incentive for the pharmaceutical companies involved to pursue additional approvals and reimbursements; this means TSC organizations are likely to play a large role in advocating for additional approvals and funding in the future.

### Priority 1 recommendations

To address the aforementioned limitations, the members of TSCi suggest the strategies in [Table 1](#), which could take the community closer to health care that implements the guidelines.

### Priority 2: People with TSC need health care that has access to TSC expertise

TSC is a complex and multisystem disease that impacts on the quality of life of both the person with TSC and their families.<sup>20,21</sup> Clinical guidelines provide a useful foundation for improved health care when they are complemented by the knowledge and skills of health professionals.

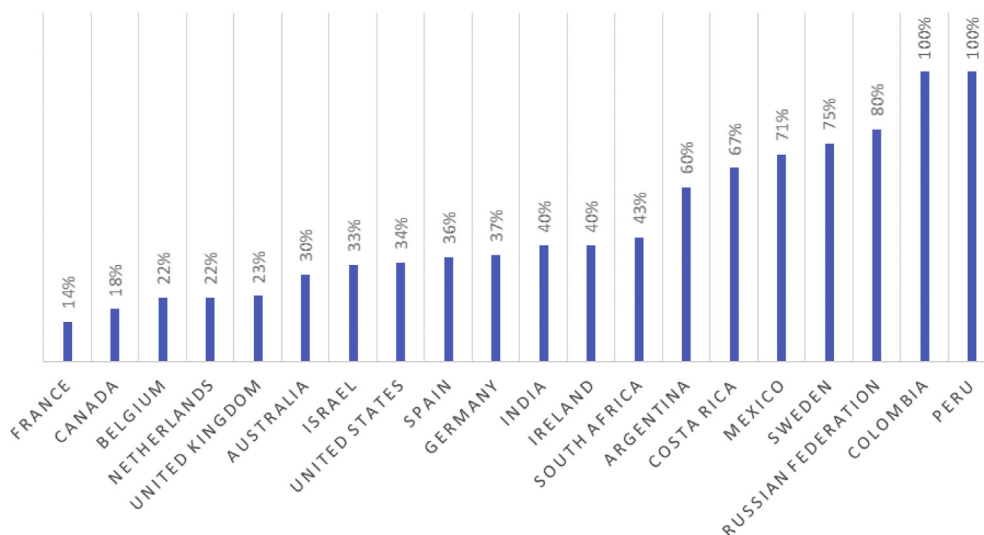
Health care for people with TSC should have the following two key components:

1. Health professionals having a basic level of up-to-date and balanced information about TSC.
2. Health professionals knowing where and how they can seek advice and reviews from TSC experts, and being willing to do so.

As research into earlier and presymptomatic treatment for TSC in infants continues,<sup>22-24</sup> timely access to TSC expertise will become a critical part of realizing the benefits of these new approaches.

Health care that has access to TSC expertise does not need to be a dedicated "one-stop shop" TSC clinic. This model of care is one that works for many people with TSC, but is often not achievable, accessible, or appropriate for many people or locations. For example, many people with TSC see a general practitioner who oversees their surveillance and engages medical specialists only

## Sharing clinical guidelines with health professionals



**FIGURE 3.** 2017 International Drug Development survey response to patient and caregiver sharing of guidelines (countries with five or more respondents). The color version of this figure is available in the online edition.

**TABLE 1.** Proposed Strategies for Guideline Implementation on International and Local Levels, Suggestions for Clinicians, and Opportunities for Future Research

TSC International collaborations	<ul style="list-style-type: none"> <li>• Investigate successes in other diseases for how international guidelines can be maintained while still implemented in different ways in different regions and settings.</li> <li>• Work with pharmaceutical companies to identify global solutions to medicines access.</li> <li>• Lead patient education on the guidelines at a global level, particularly for key information gaps such as medical warning signs, or “red flags,” for various signs of TSC.</li> </ul>
Country-level TSC organizations	<ul style="list-style-type: none"> <li>• Ensure the guidelines are available in local languages.</li> <li>• Publish information about how people with TSC and caregivers can navigate their local health system to secure health care that implements the guidelines.</li> <li>• Projects to increase awareness of guidelines among health professionals. Devries et al. documented the approach taken in South Africa to generate a country-specific consensus statement on the management of TSC.<sup>19</sup> Other country-level TSC organizations or groups of interested health professionals could adopt a similar approach.</li> </ul>
Clinicians	<ul style="list-style-type: none"> <li>• Projects to address country-specific challenges, such as working with private and public insurers to fund imaging and treatments.</li> <li>• Updates to the guidelines or supplementary publications that address specific gaps (H. Northrup et al., unpublished data, 2021).</li> <li>• Communications for patients and nonexpert TSC clinicians that explain the risks associated with not following surveillance guidelines (H. Northrup et al., unpublished data, 2021).<sup>2</sup></li> </ul>
Further research opportunities for all stakeholders	<ul style="list-style-type: none"> <li>• Registry-based projects that measure adherence to guidelines in different parts of the world, different clinical settings, and over time. Projects that provide higher-level evidence for clinical guidelines that are based on expert opinion.</li> <li>• Health economic assessments to support various recommendations, particularly imaging. For example, a cost-benefit analysis of MRI for surveillance of kidney tumours. This type of analysis could be used in various ways: for systemic advocacy by a local TSC organization to a state health care payer, for individual advocacy to a private insurance payer, or for a clinician to advocate within their institution.</li> </ul>

Abbreviations:  
 MRI = Magnetic resonance imaging  
 TSC = Tuberous sclerosis complex

when required. Others have a key specialist who liaises with other health professionals as required. For children this key specialist is often a child neurologist, and for adults, a nephrologist or a clinical geneticist.

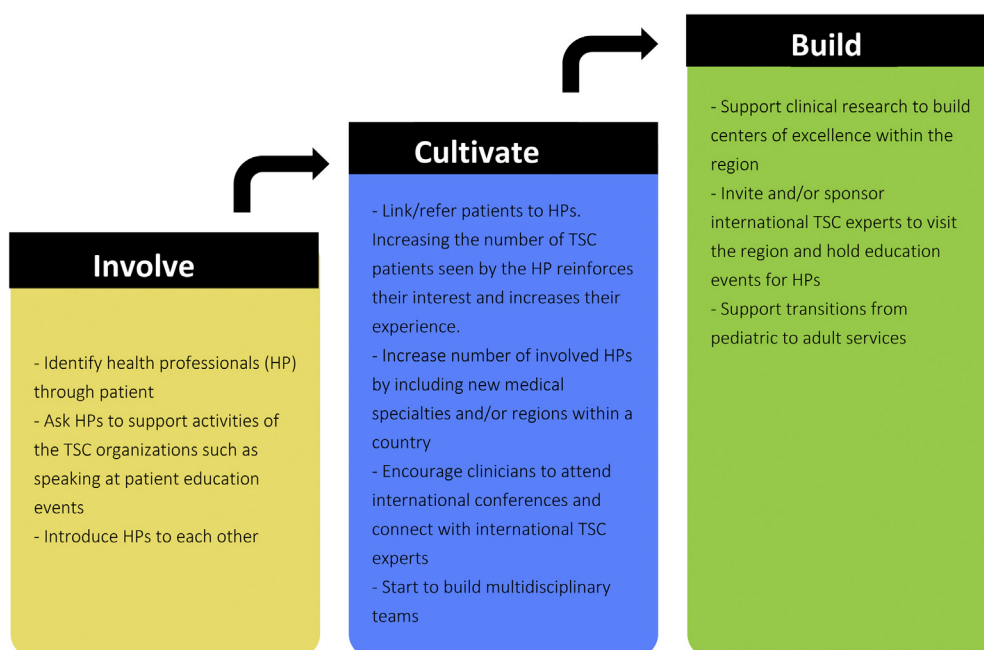
Many TSC organizations already seek to develop and improve TSC expertise in their own countries. The Improving Care project discovered that many followed a similar process with their clinician networks, working through the following three stages (Fig 4):

1. **Involve** health professionals who have an interest in TSC in the work of the local TSC organization.
2. **Cultivate** the interest of multiple health professionals in a region.

3. **Build** expertise in a region through research, funding, and education.

Although these strategies can be used to grow TSC expertise in each region, health care for a person with TSC will occasionally benefit from specific expertise beyond their regular team of health care providers. For example,

- a younger child with seizures that are not responding to first- and second-line therapies;
- an adult diagnosed with possible renal cell carcinoma by a urologist or nephrologist who is unfamiliar with TSC;
- a person with TSC with a less common sign or symptom of TSC (e.g., bone lesions<sup>25</sup>).



**FIGURE 4.** Common approach to health professional education. The color version of this figure is available in the online edition.

In these and other similar circumstances, care for the person with TSC will be improved by seeking the help of a health professional with deeper TSC expertise. Patient advocates and TSC organizations already facilitate this through informal networks and know that these connections can be lifesaving. Formalizing these networks could increase access to this expertise and allow sharing between TSC experts in different regions.

*Priority 2 recommendations*

To address the aforementioned needs, the members of TSCi suggest the strategies in [Table 2](#).

**Priority 3: People with TSC need health care that is coordinated and integrated**

One of the consistent themes that emerged from the Improving Care project was the lack of coordinated care options for people living with TSC in some countries. The nature of TSC often necessitates the involvement of a large number of professionals from various medical, allied health, education, and disability support fields. Individuals with TSC and their families often experience lack of coordination and communication between the various specialties involved in comprehensive care for an individual with TSC.

With regard to coordination of medical issues, we recognize the strengths of a multidisciplinary TSC clinic team, particularly those that have a clinic coordinator. However, many TSC clinics do not include specialists such as dermatologists, pulmonologists, and psychiatrists. TSC clinics are also often limited in their ability to integrate with allied health, education, and disability support. This limitation usually leaves caregivers and patients to take on the role of care coordinator.

The coordination of care in TSC is critical and can improve outcomes for people living with TSC. When polled to outline ideal care for a person with TSC, advocates consistently ranked coordinated care as a high priority. This conclusion has also been reached by several TSC researchers<sup>3,5</sup> and is widely understood in other chronic and complex conditions as well as in TSC, including two recently published papers by Peron et al. and Auvin et al.<sup>26,27</sup>

During this project TSC advocates identified psychiatric and psychosocial supports as particular gaps in many countries.<sup>28</sup> These gaps may be due to insufficient mental health services available in a particular region as well as the already identified underdiagnosis of TAND.<sup>23</sup> The umbrella term TAND and the TAND checklist provide a foundation for further work in this area around the world.<sup>29</sup> Individuals with TSC and their families describe ideal care as having a more holistic approach that includes both medical intervention in addition to social and family care and support.

**TABLE 2.** Proposed Strategies for Building TSC Expertise at International and Local Levels, Suggestions for Clinicians, and Opportunities for Future Research

TSC International collaborations	<ul style="list-style-type: none"> <li>• Explore feasibility of an international doctor-to-doctor expert network.</li> <li>• Continue to hold international events to connect local and international TSC expertise.</li> </ul>
Country-level TSC organizations	<ul style="list-style-type: none"> <li>• Local projects to educate health care providers. One example of this is the DEA project by the E-TSC that brings expert TSC clinicians to European countries to facilitate and promote communication between key opinion leaders and local clinicians.<sup>15</sup></li> <li>• Support patients with TSC in seeking a second opinion if needed.</li> <li>• Direct local patients with TSC to local doctors with TSC knowledge or expertise.</li> </ul>
Clinicians	<ul style="list-style-type: none"> <li>• Lead development of training opportunities such as inclusion of TSC in medical school curricula and online training opportunities.</li> <li>• When travelling for meetings, add on visits to local TSC clinicians in that country to spark interest and improve knowledge.</li> </ul>
Further research opportunities for all stakeholders	<ul style="list-style-type: none"> <li>• Evaluate opportunities for telehealth to improve care for people with TSC; this needs to explore the feasibility of telehealth across country borders.</li> </ul>

Abbreviations:  
 DEA = Disseminating Expertise and Achievement  
 E-TSC = European TSC Association  
 TSC = Tuberous sclerosis complex

The Improving Care project highlighted many differences between pediatric and adult care. The complexity of TSC health care in the absence of a suitable care coordination further complicates the transition to adult care, particularly when adults with TSC have ID and/or live in residential care<sup>26</sup>; this is consistent with other research.<sup>3,26</sup> We therefore suggest that improved care coordination has a large role to play in improving transition and reducing the number of patients lost to follow-up who may present later with life-threatening complications of TSC.

*Priority 3 recommendations*

To address the aforementioned needs, the members of TSCi suggest the strategies in [Table 3](#).

**Conclusions**

The Improving Care Project by TSCi involved TSC advocates and clinicians from several countries and identified many common themes. International diagnostic criteria and surveillance and management guidelines are crucial to improve the care of people with TSC. We recognize the global need for TSC health care that implements these guidelines, has access to TSC expertise, and is coordinated and integrated. Although the limitations of health care systems and funding are major determinants of the quality of health care for individuals with TSC around the world, there are many ways the TSC community can collaborate to ensure the outcomes of significant research investments benefit as many of the 1 million people around the world with TSC as possible.

TSC organizations around the world are vital to future progress. Country-level TSC organizations are predominantly run by volunteers who have TSC themselves or have a family member with TSC, and they are uniquely placed to understand patient and family experiences. TSC organizations are also driving change in their own countries by their existing work: encouraging TSC expertise in their local clinicians, disseminating information directly to patients and families, and by supporting TSC research projects. The majority of TSC organizations are not funded by government and rely on fundraising efforts of the local TSC community and the time of volunteers to do this work.

When these organizations come together as TSCi and are joined by leading clinicians we are able to identify shared challenges. Based on the work done through this project, TSC International organizations have identified next steps in continuing to educate and raise awareness about TSC through systemic advocacy. Collaborations are not straightforward, and success will depend on our ability to embrace our different perspectives and experiences. TSCi has built a strong network of relationships between TSC organizations as well as between health care providers around the world.

**TABLE 3.**

Proposed Strategies to Increase Access to Coordinated and Integrated TSC Care at International and Local Levels, Suggestions for Clinicians, and Opportunities for Future Research

TSC International collaborations	<ul style="list-style-type: none"> <li>• Identify models of care for TSC and other similar conditions throughout the world.</li> <li>• Facilitate connections between local health professionals to build networks between them.</li> <li>• Encourage and advocate for the development of TSC MDTs in each country.</li> <li>• Recognize health professionals and teams that provide integrated and coordinated care for people of all ages.</li> <li>• Develop guidelines for social and family care for people with TSC of all ages.</li> <li>• Consider ways to improve integration and coordination of care for individuals with TSC, such as expanding clinics or referrals to include social work and psychology.</li> <li>• Share knowledge between TSC MDTs around the world to improve care coordination.</li> </ul>
Country-level TSC organizations	
Clinicians	<ul style="list-style-type: none"> <li>• Health economics project to evaluate cost-effectiveness of coordinated care.</li> <li>• Document various models of care used by leading TSC MDTs worldwide.</li> <li>• Evaluate clinical tools such as patient logbooks and passports (electronic or manual) that can improve care coordination.</li> <li>• Increase our knowledge of the effectiveness of various TAND treatments.</li> </ul>
Further research opportunities for all stakeholders	

## Abbreviations:

MDT = Multidisciplinary teams

TAND = TSC-associated neuropsychiatric disorder

TSC = Tuberous sclerosis complex

The recommendations in this paper are high-priority areas we can act on to make a difference to the health care and the long-term health and well-being of people with TSC around the world.

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