

Supplementary Material

Table S1. Variables of Interest in the TOSCA Registry

General resources	Specific resources
Inpatient stays	
Total hospitalizations in last 12 months	related to: TSC, any other reason; Number of bed days
Each hospitalization in the last 12 months	Hospitalization: Reason, type, procedures, treatment, length of stay, ICU-ITU stays
Primary care visits in the last 12 months	
	related to: TSC, any other reason
Secondary care visits (specialists) in the last 12 months	
	related to: TSC, any other reason; Specialist: type and number of visits
Accident & Emergency (A&E) visits	
Surgical procedures	
	Procedure urgency, type and complications
Imaging tests/procedures	
	Type: CT, MRI, ultrasound, electroencephalography, angiography
Other tests	
	Type: molecular, genetic, blood, urine, neurophysiological, histology, biopsy, pulmonary function test (PFT), other.
Everolimus medication	
	Dose: initial, final, mean, median Treatment duration
Other medication	
	Type: hormonal contraception, NSAID, ACE-inhibitors, ARB, calcineurin inhibitors, diuretic beta-blocker, alfa 1-blocker, alfa 2 – agonist, calcium antagonist, mycophenolic acid compounds, inhaled beta-2 mimetics, mTOR inhibitors (not everolimus), other
Comorbidities	
	Type: cardiovascular, dyslipidemia, diabetes, liver disease, acute/chronic uncontrolled infections, autoimmune disorders, malignant tumours, other
Items that could resource in indirect costs	
	Social support/rights; Contacts with TSC associations; Education (e.g. special education needs); Patient assistance requirements (e.g. assistance at home); Employment situation for adult patients; Caregiver’s working situation for children; Family members and income for adult patients; Impact of TSC on family and self; Other

CT, computerised tomography; MRI, magnetic resonance imaging; PTF, pulmonary function test; ACE, angiotensin-converting-enzyme; ARB, antagonist receptor blockers; AE, adverse events; TSC, Tuberous Sclerosis Complex; ICU, intense care unit; ITU, intense treatment unit; NSAID, nonsteroidal anti-inflammatory drugs; mTOR, mammalian target of rapamycin.

Table S2. Potential Analyses on the TOSCA Registry

Use of resources based on clinical manifestation	
Neurological	SEGA; Cortical tuber; SEN; Cerebral white matter radial migration lines
Renal	Renal angiomyolipoma; Multiple renal cysts; Renal hamartoma; Impaired renal function; Renal malignancy
Pulmonary	Lymphangioliomyomatosis
Cardiovascular	Cardiac rhabdomyoma
Dermatologic	≥ 3 hypomelanotic macules; Facial angiofibroma; Shagreen patch; Ungual or periungual fibromas; Forehead plaque; Confetti lesions
Ophthalmologic	Retinal hamartoma
Epilepsy	Epilepsy
Use of resources based on sex	
Men - women	
Use of resources based on country	
Austria, Slovakia, Belgium, Slovenia, Czech Republic, Spain, Denmark, Sweden, Estonia, Australia, France, Israel, Germany, Japan, Greece, Korea, Italy, Russia, Latvia, South Africa, Lithuania, Mainland China, Netherlands, Hong Kong, Norway, Macau, Poland, Taiwan, Portugal, Thailand, Romania, Turkey.	
Use of resources based on country zone	
Europe - outside Europe	
Use of resources based on age at diagnosis	
Paediatric - adult	
Use of resources based on type of mutation	
By mutation type: TSC1 - TSC2 - no mutation diagnosed	
By variation type: Pathogenic mutation - variant of unknown significance	
Use of resources based on time from TSC clinical diagnosis to molecular testing	
Use of resources based on absence/presence of prenatal diagnosis	
Use of resources based on absence/presence of affected relatives/TSC inheritance	

TSC, Tuberous Sclerosis Complex; SEGA, Subependymal giant cell astrocytoma; SEN, Subependymal nodule.

Table S3. Visits to the Specialist in the Quality of Life Research Project (N=132). Analysis of healthcare visits excluding Spain (N=11) because of data inconsistencies.

	Visits to the specialist (TSC-related)	Visits to the specialist (other reason)
Patients with no visits	42 (31.8%)	69 (52.3%)
Patients with at least 1 visit	69 (52.3%)	34 (25.8%)
Patients with 1 visit	18 (13.6%)	10 (7.6%)
Patients with 2 visits	22 (16.7%)	10 (7.6%)
Patients with ≥ 3 visits	29 (22.0%)	14 (10.6%)
Patients with missing or unknown number of visits	21 (15.9%)	29 (22.0%)

Table S4. Hospitalizations over the last year in the Quality of Life Research Project (N=143)

	Hospitalizations
Patients with no hospitalizations	101 (70.6%)
Patients with at least 1 hospitalization	41 (28.7%)
Patients with 1 hospitalization	25 (17.5%)
Patients with 2 hospitalizations	7 (4.9%)
Patients with ≥ 3 hospitalizations	9 (6.3%)
Patients with missing or unknown number of hospitalizations	1 (0.7%)

Table S5. Education and Use of Social Services in the Quality of Life Research Project (N=143)

Education (children only)	Adults	Children (N=88)
The child is not in a mainstream school	n.a	28 (31.8%)
The child is in a mainstream school	n.a	57 (64.8%)
<i>Receives special education within school</i>	n.a	37/57 (64.9%)
<i>The school offers special programs adequate to the child's condition</i>	n.a	26/57 (45.6%)
Social services & benefits	Adults (N=55)	Children (N=88)
Disability allowance	21 (38.2%)	45 (51.1%)
Caregiver allowance	0 (0.0%)	10 (11.4%)
Psychological counselling	3 (5.5%)	12 (13.6%)
Social services	2 (3.6%)	4 (4.5%)
Social worker	1 (1.8%)	7 (8.0%)
Help completing benefit applications	2 (3.6%)	5 (5.7%)
Receives support with daily activities	11 (20.0%)	n.a.
Employment and finances	Adults (N=55)	Children carers (N=88)
Employed	23 (41.8%)	58 (65.9%)
Unable to work due to TSC	14 (25.5%)	8 (9.1%)
TSC has impacted on the patient's professional career	28 (50.9%)	50 (56.8%)

n.a., not available.