Tuberculosis - Prevention, diagnosis, management and service organisation – NG33

Professor Andrew Hayward

Co-Chair GDG

GDG and SDG membership ICG technical team and peer review

Guideline Development Group 2016

Ibrahim Abubakar (Guideline Co-Chair)**
Professor in Infectious Disease Epidemiology, University College London

Andrew Hayward (Guideline Co-Chair)**
Professor of Infectious Disease Epidemiology and Inclusion Health Research, University College London

Faizan Ahmed
GP, Manchester

Sudy Anaraki**
Consultant in Communicable Disease Control, North East and North Central London Health Protection Team

Christine Bell**
TB/Respiratory Nurse, Manchester Royal Infirmary

Toby Capstick (co-opted expert member)
Lead Respiratory Pharmacist, Leeds Teaching Hospitals NHS Trust

Ann Chapman
Consultant in Infectious Diseases and General Medicine, Monklands Hospital NHS Lanarkshire

Timothy Collyns
Consultant Medical Microbiologist, Leeds Teaching Hospitals NHS Trust

Francis Drobniewski
Professor of Global Health and Tuberculosis, Imperial College, London

Michael Eisenhut
Consultant Paediatrician, Luton & Dunstable Hospital NHS Foundation Trust

Mango Hoto**
Patient and carer member

Uday Katkar**
GP Locum, Stoke-on-Trent

Marc Lipman**
Consultant Respiratory Physician, Royal Free London NHS Foundation Trust

Amy McConville**
Patient and carer member

Tessa Marshall (until October 2013)
Patient and carer member, TB Alert

Philip Monk (until July 2013)
Consultant in Communicable Disease Control

Update 2016

Horace Reid**
Patient and carer member

Bertie Squire
Consultant Physician in Infectious Diseases, Liverpool School of Tropical Medicine

Alistair Story**
Consultant TB Nurse, London

John Watson – (co-opted expert member)
Consultant in Respiratory Medicine, The Leeds Teaching Hospital NHS Trust

** Guideline Development Group members who were core members of the Service delivery Group

Service Delivery Group co-optees 2016

Vanya Grant
Divisional Clinical Director for Infection, UCLH

John Hayward
Independent Consultant in Public Health, London

Alan Higgins
Director of Public Health, Oldham

Onn Min Kon
Consultant Respiratory Physician, London

Philip Monk
Consultant in Health Protection, Leicester

Ikenna Obianwa
Community Development Officer, London

For a full list of guideline development group and service delivery group declarations of interest, see Appendix A.

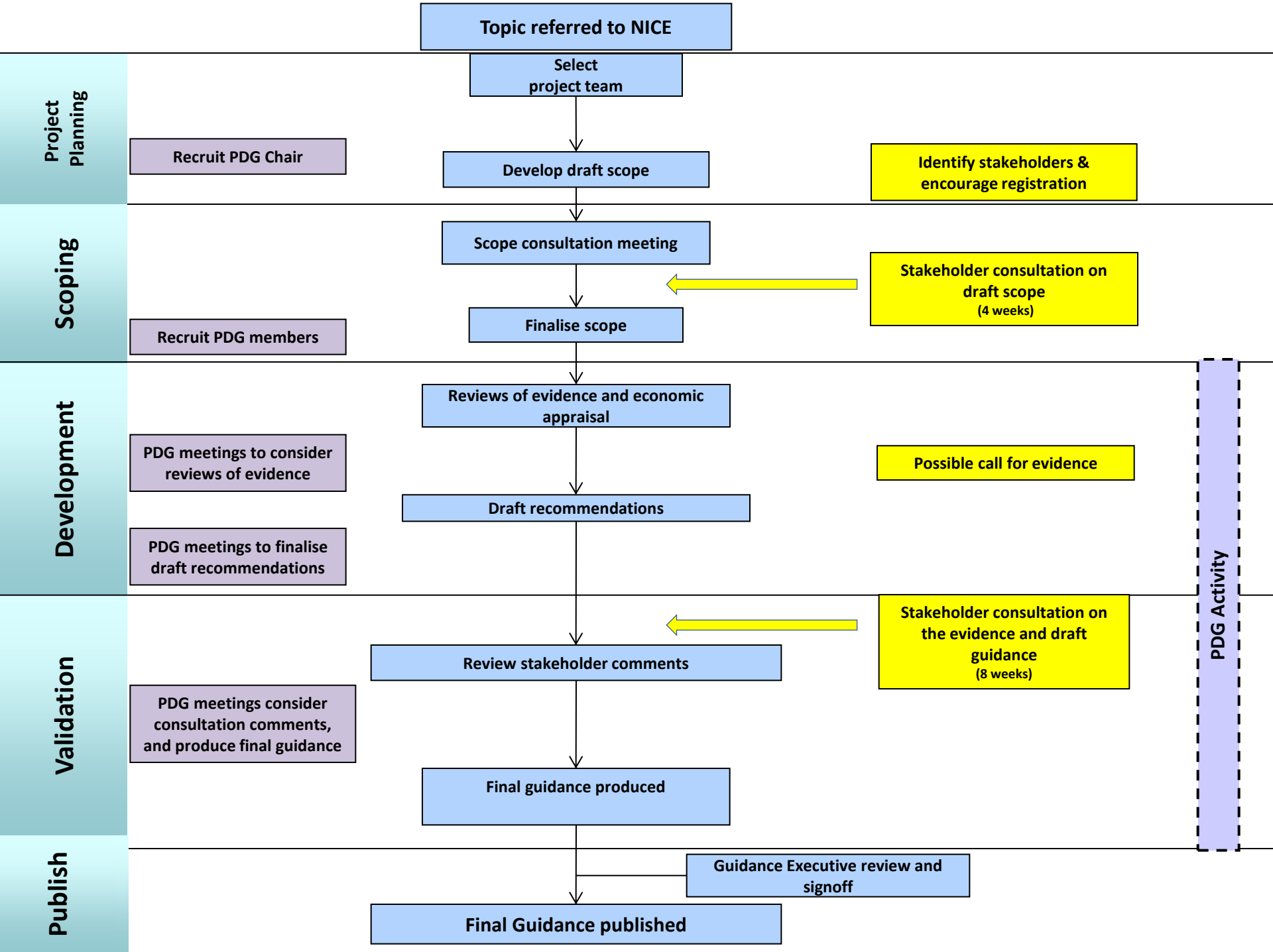
Update 2016

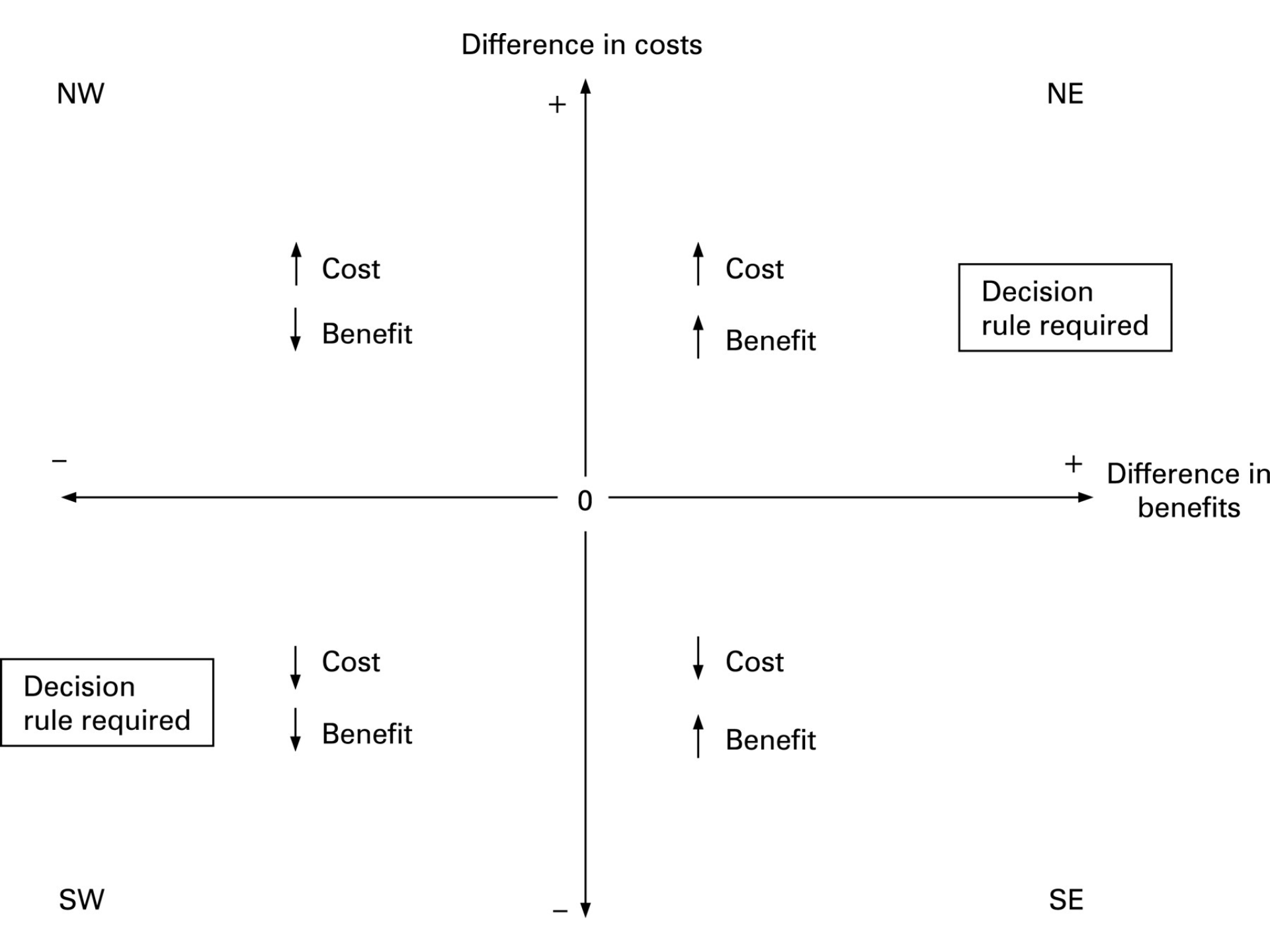
What is NICE?

The National Institute for Health and Clinical Excellence (NICE) is the ***independent*** *organisation responsible for providing national guidance on the promotion of good health and the prevention and treatment of ill health.*

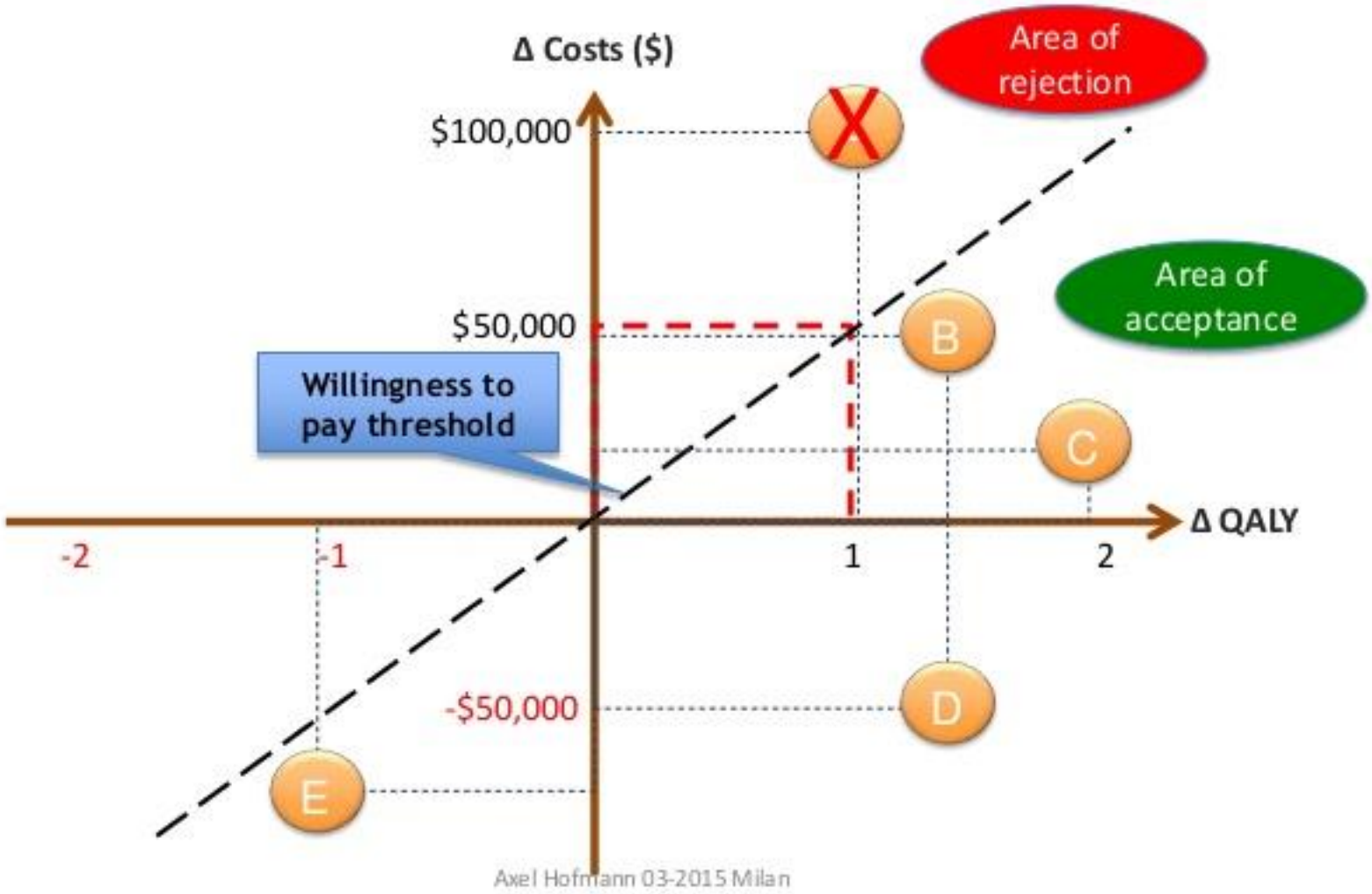
Core principles of all NICE guidance

- Comprehensive evidence base
- Expert input
- Community, patient and carer involvement
- Independent advisory committees
- Genuine consultation
- Regular review
- Open and transparent process


Topic referred to NICE
Project Planning
Select project team
Recruit PDG Chair
Develop draft scope
Identify stakeholders & encourage registration
Scoping
Scope consultation meeting
Stakeholder consultation on draft scope
(4 weeks)
Recruit PDG members
Finalise scope
Development
Reviews of evidence and economic appraisal
PDG meetings to consider reviews of evidence
Possible call for evidence
Draft recommendations
PDG meetings to finalise draft recommendations
PDG Activity
Validation
Stakeholder consultation on the evidence and draft guidance
(8 weeks)
Review stakeholder comments
PDG meetings consider consultation comments, and produce final guidance
Final guidance produced
Publish
Guidance Executive review and signoff
Final Guidance published


Difference in costs
NW
NE
+
Cost
Benefit
Cost
Benefit
Decision rule required
–
+
Difference in benefits
0
Decision rule required
Cost
Benefit
Cost
Benefit
SW
SE
–

Cost-Effectiveness Threshold



Previous guidance

- 2006 – Incorporated / Updated
- Updated 2011 (LTBI) – Largely revised based on new evidence reviews
- PH37 Hard to Reach Groups (incorporated)

Inclusions and exclusions

- LTBI diagnosis children, immunocompromised, new entrants from high incidence countries (in the context of opportunistic case finding but not population level screening).
- Occupational health issues excluded.
- BCG vaccine excluded (except uptake).

The International Gay Rodeo Association

Rodeo Calendar | IGRA Store | Event Descriptions | Animal Welfare | About Us
Local Associations | History | Gallery | Complete Menu

Upcoming Events

Oct 21-23	World Gay Rodeo Finals	Las Vegas
Nov 17-20	IGRA Convention Board Meeting (Nov 17)	Austin, TX

30th World Gay Rodeo Finals

South Point Casino in Las Vegas, Nevada
More info available here

Mantoux Change in Cut-off

- Previous cut-off was 6mm and 15mm if previous BCG. (Green Book)
- Very little evidence for this.
- Internationally 5mm is used
- Studies of effectiveness of LTBI treatment use 5mm and do not use different cut off for previous BCG.
- Studies looking at TST positivity (5mm) vs BCG status find only small increase in risk of positivity e.g. OR 1.16
- Effectiveness and Health economic analyses favoured high sensitivity - low specificity testing (Mantoux) compared to low sensitivity - high specificity scenario (IGRA) especially in children

Trade off Sensitivity and Specificity

	Has Disease	Doesn't Have Disease
Tested Positive	 True Positive Sensitivity	 FALSE Positive
Tested Negative	 FALSE Negative	 True Negative Specificity

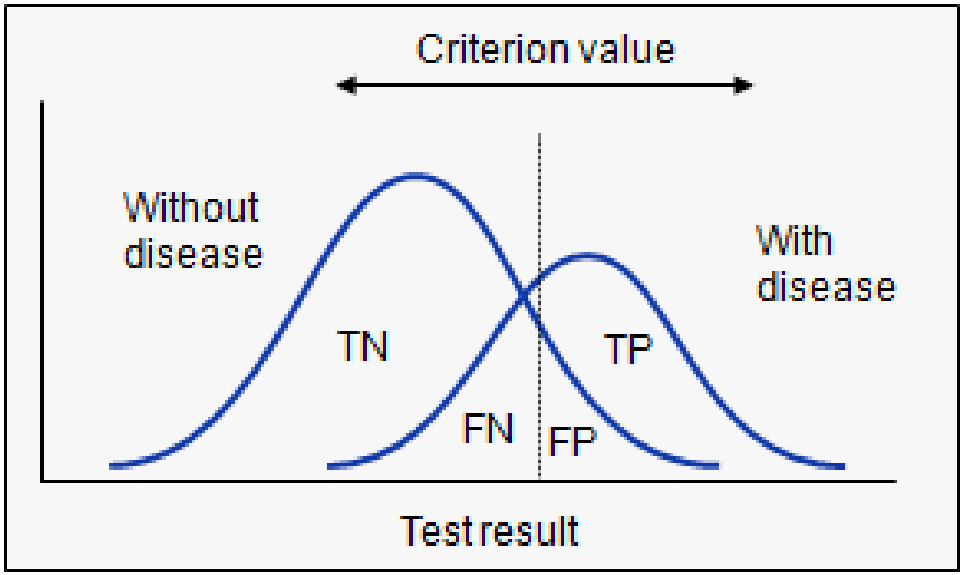


Table 12 Diagnosis of latent TB: diagnostic accuracy variables from clinical effectiveness reviews

	Sensitivity, % (95% credible interval)	Specificity, % (95% credible interval)
Children		
TST (≥5 mm)	72.80 (60.59 to 72.94)	49.03 (47.96 to 50.08)
TST (≥10 mm)	53.51 (38.21 to 67.69)	74.81 (34.34 to 76.18)
QFT-GIT	68.84 (58.56 to 78.20)	61.03 (60.30 to 61.76)
T-SPOT.TB	50.00 (2.45 to 97.64)	77.58 (67.38 to 86.40)
Immunocompromised		
TST (≥5 mm)	32.42 (11.19 to 58.48)	74.22 (72.88 to 75.57)
TST (≥10 mm)	16.82 (2.52 to 38.99)	83.97 (78.99 to 88.31)
QFT-GIT	55.48 (24.73 to 83.73)	82.27 (80.52 to 83.96)
T-SPOT.TB	66.65 (35.17 to 91.44)	68.46 (63.46 to 73.37)
Recently arrived migrants from high-prevalence countries		
TST (≥5 mm)	93.56 (77.86 to 99.77)	50.11 (47.90 to 52.29)
QFT-GIT	59.15 (35.84 to 81.42)	79.29 (77.80 to 80.73)
T-SPOT.TB	70.01 (39.78 to 92.42)	39.92 (34.39 to 45.54)

Choice of diagnostic test LTBI - Warwick Evidence Model

If you are going to test what test should you use?

Individual patient simulation was developed by Warwick Evidence to analyse the cost effectiveness of either:

- Tuberculin skin test (TST) alone – 5mm vs 10mm
- Interferon-gamma release assay (IGRA)
- Sequential TST and IGRA

In the following populations

- Children
- Newly arrived migrants from high TB prevalence countries
- Immunocompromised.

TST 5mm cutoff and if TST negative follow with IGRA was the most cost effective strategy in children

Table 13 Diagnosis of latent TB in children: base-case cost–utility results

Strategy	Mean[a]		Incremental[b]			Probability most cost effective[c]
	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	ICER (£/QALY)	
TST(≥10 mm)	300.21	23.088	–	–	–	0.032
T-SPOT.TB	332.46	23.091	32.25	0.003	Extendedly dominated	0.122
QFT-GIT	361.03	23.095	60.82	0.007	8,249	0.210
TST (≥5 mm) +ve followed by QFT-GIT	366.45	23.092	5.42	-0.003	Dominated	0.045
TST (≥5 mm)	371.14	23.096	10.11	0.001	11,255	0.269
TST (≥5 mm) -ve followed by QFT-GIT	393.03	23.097	21.89	0.001	18,871	0.322

If cost of IGRA lowered below TST then IGRA alone becomes most cost effective
If < 88% of TST are read then IGRA alone becomes most effective option.

In immunocompromised IGRA followed by TST if IGRA is negative is the most cost effective strategy

Table 14 Diagnosis of latent TB in immunocompromised people: base-case cost–utility results

Strategy	Mean[a]		Incremental[b]			Probability most cost effective[c]
	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	ICER (£/QALY)	
QFT-GIT	258.61	15.523	–	–	–	0.187
TST (≥10 mm)	269.42	15.516	10.81	−0.007	Dominated	0.046
TST (≥5 mm)	276.01	15.517	17.40	−0.006	Dominated	0.067
T-SPOT.TB	280.90	15.524	22.29	0.001	10,403	0.249
QFT-GIT +ve TST (≥5 mm)	289.31	15.516	8.41	−0.008	Dominated	0.052
QFT-GIT –ve TST (≥5 mm)	318.26	15.526	37.36	0.002	18,746	0.399

If return rate for reading of TST is <75% then IGRA alone becomes the most cost effective option.

In migrants from high incidence countries TST 5mm was the most cost effective

Table 15 Diagnosis of latent TB in recently arrived migrants from high-prevalence countries: base-case cost–utility results

Strategy	Mean[a]		Incremental[b]			Probability most cost effective[c]
	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	ICER (£/QALY)	
QFT-GIT	291.13	19.917	–	–	–	0.177
TST (≥5 mm)	298.75	19.922	7.62	0.005	1,524	0.469
TST (≥5 mm) +ve QFT-GIT	300.10	19.909	1.35	-0.013	Dominated	0.032
TST (≥5 mm) -ve QFT-GIT	353.47	19.923	54.72	0.001	58,720	0.28
T-SPOT.TB	400.12	19.915	46.65	-0.008	Dominated	0.042

Adding IGRA if TST negative marginally increased QALYS but at a cost above the threshold for cost effectiveness.

If probability of TST being read drops below 76% then IGRA alone becomes most cost effective strategy

The increased risk of death from TB when using a low sensitivity - high specifity strategy outweighs the risk of death from hepatoxicity when using a high sensitivity low specificity strategy.

High sensitivity
Low Specificity
(TST)

1 more death
from hepatitis

Low sensitivity
High Specificity
(IGRA)

6.3 more deaths
from TB

Imperial College London – Model for treatment of LTBI

- In people diagnosed with LTBI who should be treated and with what regime?
- Four age-groups (17–34 years, 35–50 years, 51–65 years, 66–86 years)
- Adverse events increase with age
- Lifetime risk of progressing from LTBI to active disease decreases with age due to shorter life expectancy
- Case fatality rate of TB higher in the elderly

The risk of death from TB in older adults who are not treated for LTBI outweighs the risk of death from hepatotoxicity through LTBI treatment.

Risk of death from hepatotoxicity due to chemoprophylaxis are 5.5 times higher in those aged 51-65 than those aged < 35

Risk of death if develop TB is 4 times higher in those aged 45-64 than in those aged 15-44

Treating all people under the age of 65 with 6H or 3HR would lead to net health gain at a cost of less than £20,000 per QALY gained, compared with no treatment.

Treatment LTBI

- Treatment of LTBI with 6H or 3HR at all ages leads to net health gains
- For those under the age of 65 the cost per QALY is less than £20,000
- For those over the age of 65 the cost per QALY is greater than £20,000
-
- Cost effectiveness is highly sensitive to the costs of treatment support.

Groups at high risk of progression

- are HIV-positive
- are younger than 5 years
- have excessive alcohol intake
- are injecting drug users
- have had solid organ transplantation
- have a haematological malignancy
- are having chemotherapy
- have had a jejunoileal bypass
- have diabetes
- have chronic kidney disease or receive haemodialysis
- have had a gastrectomy
- are having treatment with anti-tumour necrosis factor-alpha or other
- biologic agents
- have silicosis

Close Contacts

- Offer Mantoux testing to diagnose latent TB in adults aged 18 to 65 who are close contacts of a person with pulmonary or laryngeal TB.
- If the Mantoux test is positive but a diagnosis of active TB is excluded, consider an IGRA if more evidence of infection is needed to decide on treatment. This could be, for example, if the person needs enhanced case management or if there could be adverse events from treatment.

Children

- Only consider using interferon-gamma release assays alone in children and young people if Mantoux testing is not available or is impractical. This includes, for example, situations in which large numbers need to be tested

Children close contacts

- Guidance for children under 2 years who are contacts of smear positive TB. Emphasizing early treatment of LTBI and step down if infection ruled out by TST and IGRA.
- Refer children younger than 2 years and in close contact with people with smear-negative pulmonary or laryngeal TB to a specialist to determine what testing strategy for latent TB should be done.
- For children > 2years – Start with Mantoux – if negative also use IGRA.

New entrants – who present to health services

- Mantoux (or IGRA if Mantoux not available)
- Offer treatment if <65
- Consider offering BCG for unvaccinated people who are Mantoux- or IGRA negative
- Regardless of when they arrived in England. People born in countries with an incidence of more than 150 per 100,000 per year should be made a priority for latent TB testing when they arrive here.

Immunocompromised

- Severely immunocompromised
  - Mantoux with concurrent IGRA
- Less immunocompromised
  - IGRA alone or concurrently with Mantoux

Treatment regimes LTBI

- 3 months of isoniazid (with pyridoxine) and rifampicin or
- 6 months of isoniazid (with pyridoxine)
- For adults between the ages of 35 and 65 years, offer drug treatments only if hepatotoxicity is not a concern.
- Base the choice of regimen on the person's clinical circumstances:
- 3 HR to people younger than 35 years if hepatotoxicity is a concern
- 6H if interactions with rifamycins are a concern, for example, in people with HIV or who have had a transplant

Box 2: Infection control measures ***[Updated recommendations 2016]***

- Minimise the number and duration of visits a person with TB makes to an outpatient department while they are still infectious

- Put people with suspected infectious or confirmed pulmonary or laryngeal TB who will remain in hospital in a single room. If this is not possible, keep the person's waiting times to a minimum. This may involve prioritising their care above that of other patients

- Do not admit people with suspected infectious or confirmed pulmonary TB to a ward containing people who are immunocompromised

- Explain to inpatients with suspected infectious or confirmed pulmonary or laryngeal TB that they will need to wear a face mask whenever they leave their room. Ask them to continue wearing it until they have had at least two weeks of treatment

- Offer patients advice on simple respiratory hygiene measures, such as covering the mouth and nose with a tissue when coughing or sneezing and disposing of the tissue in a waste basket

- For people deemed to be at high risk of multidrug resistance, provide care in a negative pressure room

- Staff and visitors should wear FFP3 face masks during contact with a person with suspected or known multidrug resistant TB while the person is thought to be infectious

Box 4: Treatment regimen for active TB ***[Reviewed, not amended, 2016]***

- For people with active TB without central nervous system involvement, offer
  - –Isoniazid (with pyridoxine), rifampicin, pyrazinamide, and ethambutol for two months, *then*
  - –Isoniazid (with pyridoxine) and rifampicin for a further four months
- For people with active TB of the central nervous system, offer
  - –Isoniazid (with pyridoxine), rifampicin, pyrazinamide, and ethambutol for two months, *then*
  - –Isoniazid (with pyridoxine) and rifampicin for a further 10 months
- Modify the treatment regimen according to drug susceptibility testing

Multidrug resistant TB

- Request rapid diagnostic NAATs for rifampicin resistance if risk factors for multidrug resistance are identified:
  - –Previous TB drug treatment, particularly with poor adherence
  - –Contact with a known case of multidrug resistant TB
  - –Birth or residence in a country in which the World Health Organization reports that a high proportion (≥5%) of new TB cases are multidrug resistant (fig 2⇓).[5]
  - Start infection control measures (see box 2). *[Updated recommendation 2016; based on low quality cross sectional studies and the experience and opinion of the GDG]*
- If the NAAT for rifampicin resistance is positive
  - –Continue infection control measures until pulmonary or laryngeal disease has been excluded
  - –Manage treatment along with a multidisciplinary team with experience of managing multidrug resistant TB
  - –Offer treatment with at least six drugs to which the mycobacterium is likely to be sensitive
  - –Test for resistance to second line drugs.

New entrant LTBI screening In practice. TB in England 2016 report

- £10 million allocated to new entrant LTBI screening in 2015/16
- Offered IGRA – 5622 (£1778 per offer)
- Tested with IGRA – 2904 (£3443 per test)
- Positive IGRA – 510 (£19607 per positive test)
- Agree to start tx – 256 (£39062 per treatment)

- Number eligible > 400,000

Box 5: Enhanced case management for TB *[Updated recommendations 2016]*

- This comprises a package of supportive care tailored to the person's needs, for someone with clinically or socially complex needs
- DOT is offered as part of enhanced case management in people who
  - –Do not adhere to treatment (or have not in the past)
  - –Have been treated previously for TB
  - –Have a history of homelessness or drug or alcohol misuse
  - –Are in prison or have been in the past five years
  - –Have a major psychiatric, memory, or cognitive disorder
  - –Are in denial of the TB diagnosis
  - –Have multidrug resistant TB
  - –Request DOT after discussion with the clinical team
  - –Are too ill to administer the treatment themselves.

Virtually Observed Therapy (VOT)

Important Phone Numbers

If you are experiencing problems with your medication or you are feeling unwell with new or worsening side effects (see back of the pill chart) call your TB Case Manager or health care provider immediately. If this is a medical emergency, call 999.

TB Clinic :
Name:_____
Phone:_____

TB Case Manager:
Name:_____
Phone:_____

General Practitioner (GP) :
Name:_____
Phone:_____

TB Case Worker:
Name:_____
Phone:_____

If you are experiencing technical problems with your phone, call the TB Reach study team on: 020 3549 5556/5554 or email rfh.tbreach@nhs.net

UCL | National Institute for Health Research | Royal Free Hampstead NHS Trust | TB Reach

Patient Recording Procedure

Study No.:_____

TB Reach

Recording Procedure

1. Gather medications on pill chart, water, and mobile phone in well-lit location.

2. Turn phone on and set it up horizontally in front of your face on a flat surface.
   Note: Phone must be horizontal to record videos. (see picture on front page)

3. Press the VOT icon on the Home Screen.

4. In the application, press the "Record" button. Make sure you can see your face clearly on the screen.

5. To begin recording, press the **GREEN** button on the top right of the screen.

6. Say your study number (on front page) and where you are. Specify the number, and type of pills by name and dosage OR size, shape and color
   e.g: I am taking 5 round pink, 2 round grey, 2 small yellow and 1 small round white pill.

7. a) Show the first pill in front of camera and say the name and dosage OR size, shape and color

   b) Show pill(s) on tongue, and your empty hand. Drink.

   c) Swallow pills and show empty tongue up and down.

Video Confirmation

8. Repeat Step 7 (a, b and c) until all types of pills are taken.

   Note: Take a maximum amount of four pills in one go. Show all of them on the tongue before swallowing.

9. Please report on the video if you:
   a) do have or don't have any side effects (see back of pill chart).
   b) have any technical problems with your phone.

10. To end recording, press the **RED** button on the top right of the screen.

11. When recording stops, video is automatically sent to the VOT observer.

12. A status bar will appear showing the progress of your video upload.

13. To check the status of your video from the home screen, press the "Status" button.

Your video uploads will appear as follows:

Blue: In-Progress

Green: Successful

Note: For privacy, you can view the status, but not the videos themselves.
If your video does not upload successfully, first check that your Wi-fi is "OFF".