Public slides

NICE National Institute for Health and Care Excellence

Ibrutinib for treating Waldenstrom's Macroglobulinaemia [ID884]

2nd Appraisal Committee Meeting

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Preliminary recommendation

- Ibrutinib is not recommended within its marketing authorisation for treating Waldenstrom's macroglobulinaemia in adults who have had at least one prior therapy or as first-line treatment when chemo-immunotherapy is unsuitable.

  ACD, section 1.1

Ibrutinib

- Ibrutinib is indicated for the treatment of adult patients with Waldenstrom's macroglobulinaemia (WM)
  - who have received at least one prior therapy, or
  - in first line treatment for patients unsuitable for chemo-immunotherapy (May 2015)
- Ibrutinib is an oral monotherapy administered until disease progression or until the treatment is no longer tolerated by the patient.
- Ibrutinib inhibits BTK proteins to stop B-cell (lymphocyte) proliferation and promotes cell death

ACD conclusions: Clinical need

- The committee concluded that:
  - there is no standard of care for treating WM and treatment tends to combine rituximab with a range of chemotherapy options
  - WM is a rare and very debilitating disease that is associated with a high unmet clinical need for new effective therapies
  - WM treatment options have been reduced - bortezomib and stem cell transplant no longer funded
  - the availability of a highly targeted, effective and well tolerated oral therapy is highly valued by patients and addresses a significant unmet need among people with WM

ACD conclusions: Clinical effectiveness

- The committee concluded that:
  - the trial (PCYC-1118E) was of a reasonable quality and generalisable to UK clinical practice, but was limited by the lack of a comparison against a treatment used in the UK. It was suitable for decision making.
  - ibrutinib is associated with high response rates and high progression-free survival and overall survival rates at 2 years but the longer-term effects on progression and survival are uncertain because no data is available
  - based on the testimonies from patients and clinical experts, ibrutinib appears to be more clinically effective than existing treatments but there is uncertainty about the size of the benefit

Clinical effectiveness

- One single-arm, open-label trial in the US (study PCYC-1118E). This included 63 adults with WM who had had at least one prior therapy.

Summary of results

Overall response rate	90.5% (95% CI: 80.4 – 96.4)
Major response rate (MRR)	73.0% (95% CI: 60.3 – 83.4)
Progression free survival (PFS)	Median PFS has not been reached. At 24 months, the estimated rate of PFS was 69.1% (95% CI: 53.2 – 80.5)
Overall survival (OS)	Median OS has not been reached. At 24 months, the estimated rate of OS was 95.2% (95% CI: 86.0 – 98.4)
Duration of response	Not reached

Clinical effectiveness: Indirect comparison using patient-level efficacy data from the pan-European chart review study

- A “matched” cohort was created by selecting a subset of the overall pan-European chart review cohort that had received similar prior lines of therapy as study PCYC-1118E (175 of the 454 patients were selected). Patients who received 5 or more lines of therapy were excluded from the analyses (patients included from PCYC-1118E = 47)
- The company’s multivariable Cox proportional hazards model produced an estimated hazard ratio (HR) for PFS for ibrutinib versus standard therapies of [redacted]([redacted])

Clinical effectiveness: Indirect comparison using patient-level efficacy data from the pan-European chart review study (2)

PFS curves of ibrutinib vs. matched chart review cohort

ACD conclusions: Cost effectiveness

- The committee understood that the model did not include treatment-naïve patients for whom chemo-immunotherapy was considered unsuitable, therefore it could not reliably assess the cost effectiveness of ibrutinib in this group of patients
- The committee was mindful of limitations within the model structure but concluded that it was acceptable for decision making
- For patients with relapsed or refractory WM, the committee concluded that:
  - it could not determine how pre-progression mortality in the comparator arm was estimated, and this uncertainty impacted on the cost-effectiveness estimates produced in the economic model
  - there was considerable uncertainty around the estimation of overall survival in the ibrutinib arm, and the issue of pre-progression mortality was a concern that merited further consideration
  - given these uncertainties it could not identify the most plausible incremental cost effectiveness ratio (ICER)
  - company's ICERs (base case £58,600 per quality-adjusted life year (QALY) gained and above £47,000 in all sensitivity analyses) were substantially above the range considered a cost-effective use of NHS resources, that is, £20,000 to £30,000 per QALY gained

Cost effectiveness results

Scenario	ICERs
Company base case	£58,630
ERG base case (Included use of ibrutinib pre-progression mortality rates from Study 1118E instead of general population mortality rates and re-estimation of drug cost)	£61,050
ERG exploratory analyses	
Assume best supportive care utility value to be 0.5 instead of 0.665	£63,340
Use of alternative hazard ratio of [redacted] for progression free survival (PFS) from company's repeated analysis instead of [redacted]	£60,410
Assumption of equivalent pre-progression mortality for ibrutinib and rituximab/chemotherapy	£390,432
Use of alternative costs for rituximab/chemotherapy	£64,233
Use of the Weibull distribution for pre-progression mortality for rituximab/chemotherapy	£64,628
Threshold analysis around hazard ratios for PFS	£56,917* £59,620**

All ICERs displayed were estimated with a simple discount patient access scheme. The discount was subsequently updated which reduced the company's base case ICER to £49,021.

* the most favourable ICERs possible given any HR for PFS (using company's base case assumptions)
** the most favourable ICERs possible given any HR for PFS (using ERG's base case assumptions)

ACD: Other conclusions

Innovation

- The committee accepted that ibrutinib could be considered a step change in managing WM

Cancer Drugs Fund

- The ICERs presented were well above the level which could be accepted as a cost-effective (can only be referred to CDF if the ICERs presented have the *plausible potential* for satisfying the criteria for routine use, taking into account the application of the End of Life criteria where appropriate)
- The committee also heard from the clinical experts that an additional 2 years of data collection was unlikely to be long enough to collect meaningful progression or survival data
- The committee concluded that ibrutinib for treating WM does not have the plausible potential to be cost effective in routine commissioning and cannot be recommended for inclusion in the Cancer Drugs Fund

End of life

- The company did not present a case that ibrutinib meets NICE's criteria for life extending therapies given at the end of life. If the criteria is met it allows the committee to accept a different QALY weighting (*NICE Methods guide*)

Criterion	Data available
Short life expectancy, <24 months	✗ Median OS: • ranges from less than 4 years to 12 years (company submission) • 123 months (Pan-European chart review)
Offers an extension to life, ≥ 3 months	Unknown at present

Background to committee decision making

- Committees have to approach decision making in line with '*NICE Guide to the methods of technology appraisal'* to ensure equity and consistency of decisions.
- Committee cannot ignore the cost effectiveness evidence and make decisions only on the clinical effectives
- The committee agreed that ibrutinib is an effective, innovative and targeted treatment for a rare disease with high unmet need, but the (updated) price still results in a very high ICER of £54,000 per QALY gained

Key decisions

- Can the committee accept an ICER of £54,000 per QALY gained?
  - £20-30,000 per QALY is the usual range of cost effectiveness (*NICE Methods guide)*
  - What would be the grounds for doing so?
- What is the committee's view on the company's modelling approach?
  - Is it based on the correct comparators?
  - Are assumptions about long term treatment options reasonable?
- What is the committee's view on the size of clinical benefit of ibrutinib?
  - Could it have been underestimated, how would this impact the ICER?
- Does the committee consider that the relative treatment costs have been overestimated?

Key decisions (2)

- Does the committee consider the clinical and cost-effectiveness estimates generalisable to treatment naïve patients for whom chemo-immunotherapy is unsuitable?
- Can the small patient population and limited budget impact be taken into account?
- Does ibrutinib for treating WM satisfy the criteria of an end of life treatment?
- Are there any innovative aspects of ibrutinib not captured by the QALY? If so, would their inclusion bring the ICER within a range that would be considered a cost effective use of NHS resources?
- Is ibrutinib for treating WM a suitable candidate for the Cancer Drugs Fund?

ACD Consultation comments

Comments were received from:

- The company (Janssen)
- Lymphoma Association
- Leukaemia CARE
- WMUK
- Clinical experts

Company's revised base case

- The company's revised base case incorporates changes to:
  - pre-progression mortality in the physicians choice arm
  - pre-progression mortality in the ibrutinib arm
  - projection of progression-free survival in the ibrutinib arm
  - drug acquisition costs in the physicians choice arm
- Includes increased patient access scheme discount

Revised base case	Total cost	Total QALYs	Inc Costs	Inc QALYs	ICER
Physician's Choice	[redacted]	[redacted]	[redacted]	[redacted]	
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	54,141

Company's comments (1)

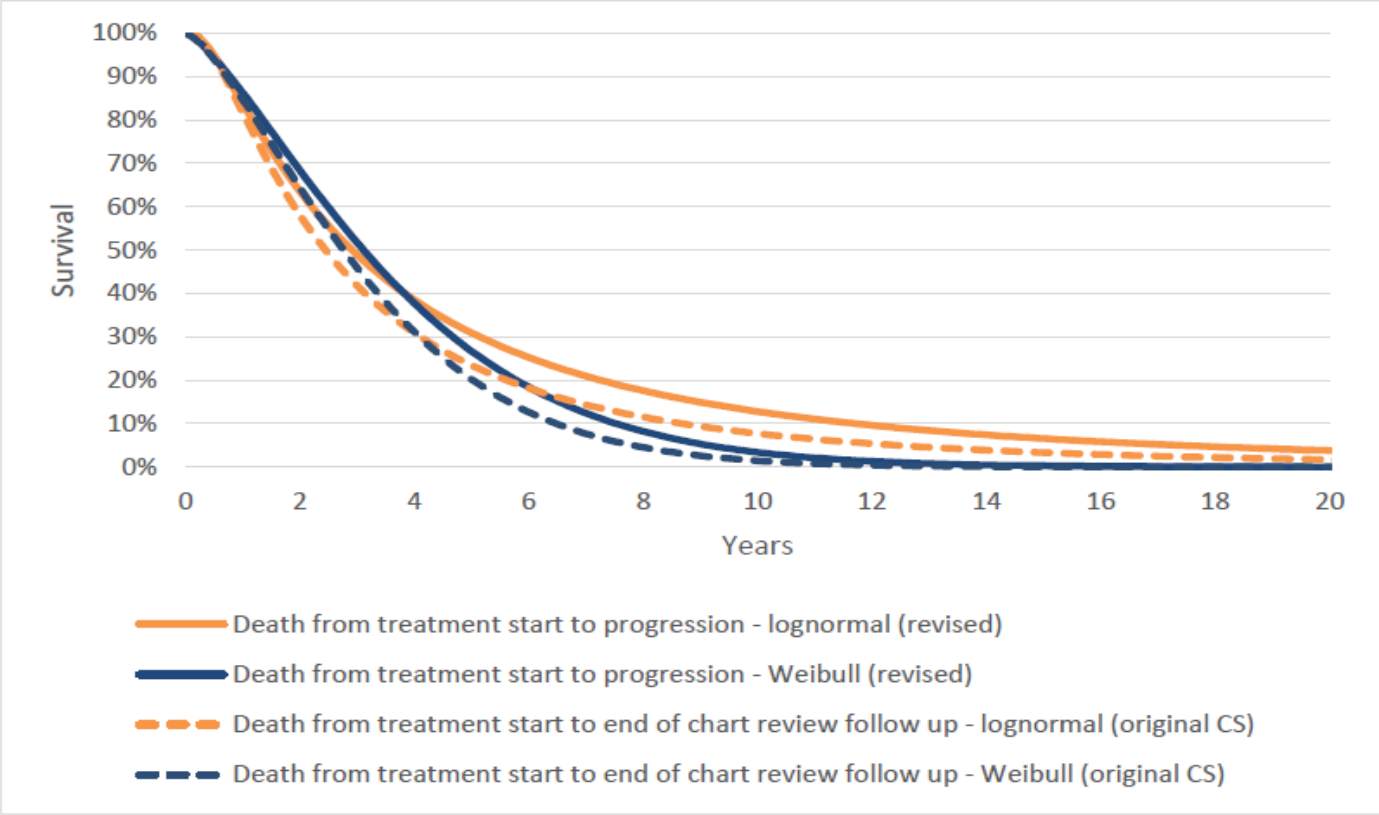
Modelling of pre-progression mortality – Physicians choice (PC)

- In the original company submission, pre-progression mortality was estimated based on deaths that occurred during the full observation period (from start of the last line of treatment until the end of follow-up). Therefore, pre-progression deaths could have included those that occurred during a "watch and wait" period.
- The uncertainty associated with pre-progression mortality can be resolved with further real-world data collection.
- In the revised model, pre-progression mortality for physicians choice was derived using a narrower observation window where the point of progression (and not the start of next line of treatment) was used as the 'cut-off' point for collecting pre-progression mortality data. As a consequence, death occurring after patients have progressed but whilst they are in the "watch and wait" period (i.e., not yet commenced the next line of treatment) is no longer used to derive the pre-progression risk of death.

Company's comments (2)

- The revised estimate reflected slightly lower mortality than in the original company submission

Comparison of pre-progression mortality curves for PC



Company's comments (3)

Modelling of pre-progression mortality – ibrutinib arm

- The company consider the ERG's analysis that assumed equivalent pre-progression mortality between ibrutinib and PC to be clinically implausible
- The company's model assumed general population mortality rates for the ibrutinib arm. However, they revised the model to:
  - assume constant hazard - based on PCYC-1118E data
  - this is assumed until the general population mortality exceeds the constant hazard
  - after which it assumes the general population mortality rates

Company's comments (4)

Matched cohort – comparative effectiveness

- The company highlighted that 4 approaches were taken to estimating comparative effectiveness (the primary analysis and 3 scenario analyses), producing hazard ratios varying from [redacted] to [redacted], with all 95% confidence intervals remaining significant
- These estimates:
  - provide the strongest available evidence of a consistent treatment benefit associated with ibrutinib when compared with physician's choice
  - demonstrate that multiple approaches were taken, all resulting in a clinically and statistically significant benefit that cannot be ignored

Company's comments (5)

Treatment naive population

- The company has asked the committee to reconsider its recommendation in relation to treatment-naïve patients for whom chemo-immunotherapy is considered unsuitable
- Very difficult to collect data in this cohort
- It impacts older people for whom chemo-immunotherapy is more likely to be unsuitable, limiting their options further

Corrections

- Drug acquisition costs of fludarabine, cyclophosphamide and rituximab have been corrected
- Found no other modelling errors identified by the ERG

New supporting clinical evidence

The company submitted additional data now available from studies Study PCYC-1118E and the iNNOVATE trial

37-month follow-up from PCYC-1118E (n=63)

- Estimated rate of PFS: 82.0% (95% CI, 69.1 to 89.9)
- Estimated rate of OS: 90.0% (95% CI, 77.4 to 95.8)

Arm C iNNOVATE trial poster presentation at EHA 2016

- Non-randomised arm of the Phase III study of rituximab-refractory WM patients
- At a median follow-up of 17.1 months the overall response rate = 90%, major response rate = 71%.
- PFS at 1-year was 93%

Company concluding comments

- The PFS of ibrutinib has been consistently demonstrated across a number of scenarios using rigorous and commonly-used approaches that utilise two patient-level data sets in a space where clinical data are severely limited
- The opportunity to collect additional data through the CDF (e.g. PFS). Would be an invaluable opportunity to:
  - confirm ibrutinib's treatment effect
  - test the most extreme scenarios put forward by ERG
  - add to the evidence base in this rare patient population
- The revised economic analysis provides reasonable alternative approaches to inform pre-progression mortality for the PC and ibrutinib arms and does not result in significantly different health outcomes.

Lymphoma Association comments

General comments

- Disappointed with the recommendation
- Overwhelming support for the use of ibrutinib
- Concern over the appraisal process, especially with rare disease areas
- Do not understand why NICE and the company cannot reach a mutually acceptable arrangement

Specific concerns

- ***Health economics*** – The ERG used a comparison model that is inappropriate
- ***Generalisability*** – Concern with ERG's view of the pivotal trial. The trial data should be accepted even though it is US based with a small population

Lymphoma Association comments (2)

- ***Pricing*** – It was clearly a problem, why can't this be dealt with earlier in the process?
- ***Cost impact*** – Overall cost to the NHS would be modest with such a small population
- ***Uncertainty*** – Rarer cancers with small populations are likely to have greater levels of uncertainty. Working with the same thresholds of uncertainty means reduced opportunities in these disease areas

NICE Guide to the methods of technology appraisal

Pricing

- NICE does not set or negotiate the price of a technology. It evaluates the value proposition presented by a company
- When there are nationally available price reductions… the reduced price should be used in the reference-case analysis to best reflect the price relevant to the NHS.(Methods guide 5.5.2)

Cost impact

- The potential budget impact of the adoption of a new technology does not determine the Appraisal Committee's decision. The Committee does take account of how its advice may enable the more efficient use of available healthcare resources (Methods guide 6.2.14)

Uncertainty

- There are always likely to be deficiencies in the evidence base available for health technology assessment…Therefore, analyses should be explicit about the limitations of the evidence, and attempts to overcome these, and quantify as fully as possible how the limitations of the data are reflected in the uncertainty in the results of the analysis. (Methods Guide 3.2.2)

Leukaemia CARE comments

- There are limited treatment options for WM, creating a severe unmet need
- WM is a rare, chronic debilitating condition. Ibrutinib can address the symptom burden and allow patients to return to their normal lives
- Ibrutinib is an innovative treatment, considered a step-change in the treatment of WM. It would be welcomed by patients.
- Ibrutinib demonstrated good response rates and improved survival estimates. Acknowledges the uncertainty in the data but considers that it is due to the innovative nature of ibrutinib
- The conclusion that 2 years of data collection is “unlikely to be long enough to collect meaningful progression or survival data” discriminates against the rare and chronic conditions, where there is often the greatest uncertainty

WMUK comments

General comments

- WMUK welcomes the recognition from the committee that ibrutinib is a targeted therapy that would be valued by patients and clinicians

Specific concerns

- ***Administration*** – Concern over the administrative aspects of the committee. Doubts over whether patient views, clinical evidence, and cost effectiveness evidence has been considered appropriately.
- ***Health economics*** – ERG's output used a comparison model suited to conventional single chemotherapy rather than one based on a chronic condition. Unsuited to capturing the economic value to patients, carers and society in transforming patients into economically active citizens
  - For the reference case, the perspective on outcomes should be all direct health effects, whether for patients or other people. The perspective adopted on costs should be that of the NHS and personal and social services. (Methods guide, 5.1.7)

WMUK comments (2)

- ***Clinician support*** – The strength of clinical support is muted in the ACD. The clinical letter of support was redacted and the survey received no comment
- ***Genetic targeting*** – No mention in the ACD summary of the specific genetic targets in WM
- ***Treatment effects*** – The limitations of all potential treatments have not been capture in the ACD
- ***Treatment-naïve patient*** – ERG and ACD are overly concerned with the uncertainty of treatment effect in treatment-naïve patients. Evidence presented by Dana Farber trial demonstrate the expected effect in treatment-naïve patients. The EMA accepted the rational that a similar effect is expected in treatment naïve patients.
- ***ERG View of Dana Farber trial*** – ERG are overly critical of the trial. The ACD makes no concession to the rareness of the disease and the difficulty in collecting data in these populations.

WMUK comments (3)

- ***Pricing*** – Lower price was on the table that would have achieved an acceptable ICER. There were doubts over pricing, so why not postpone the meeting until price confirmation.
- ***Uncertainty*** – Uncertainty inherent in rare disease trials but there are contradictions. Uncertainty is 'stressed' by the ERG but they were certain that CDF would not reduce uncertainty.
- ***End of life and rareness*** – Under Scottish Medicines Consortium rules Ibrutinib would probably be classed as an end of life treatment.
- ***CDF overlooked*** –The clinical data registry has been set up to collect real time patient reported outcomes and already has over 300 patients. Concern that the clinical need for this study was not considered before the CDF option was abruptly dismissed. Considers that progress would be made in 2 years and expresses concern over how any technology could be admitted to the CDF

WMUK comments (4)

- ***Lack of focus on WM by NICE*** – WM is using off-label drugs with very few options. Recent clinical guidelines from NICE (*Non-Hodgkin's lymphoma: diagnosis and management,* NG52) did not include WM. This discriminates against WM where treatment options have reduced.
- ***Rareness*** – Acceptance of ICERs up to £100,000 per QALY gained in ultra-rare diseases. Ethically and clinically, why should £30,000 per QALY gained be the upper limit for 'just' rare diseases? Where is the rare diseases / ultra-rare diseases boundary set?
- ***Other B cell cancers*** – Concern that NICE and NHS is focused on cost reduction and linking this STA to wider discussion on ibrutinib pricing
- ***Cost impact –*** The cost impact to the NHS in year 1 is <£6m, minus current treatment costs and not including economic benefit to the patient and society. This falls below 'budget impact threshold' of £20m' (NICE, Oct 2016).
- ***Innovation*** – Can NICE deliver its promise to make innovative medicines rapidly available for rarer diseases?

Clinical expert 1 comments

General comments

- Robust evidence review that was fair, accurate and representative
- Believes the ibrutinib should be available for patients with relapsed and refractory WM to address a significant unmet clinical need

Specific issues

- ***Equality issues*** – The low toxicity of ibrutinib compared with chemotherapy, often not tolerated by older people needs to be taken into consideration.
- ***Model*** – "Acceptable for decision making", not perfect but the committee was willing to use it for the basis of this decision.
- ***Subgroup*** – Clinically significant advantage for older people.

Clinical expert 1 comments (2)

Cancer Drugs Fund

- Survival data unlikely to be forthcoming but important PFS, QALY, and adverse event data can be accrued over a 2 year collection period
- Already an existing registry
- CDF criteria unfamiliar at 1st meeting. More prepared to explain the information that can be gathered in the registry
- Incorporating a genomic profile into the data collection process will provide the opportunity to interrogate subgroups of WM patients
- May not translate into a more favourable cost effectiveness estimate

Clinical expert 2 comments

General comments

- Disappointed that ibrutinib has not been recommended
- Pleased that the committee recognised the debilitating nature of the condition, the unmet clinical need, limited options, novel targeted innovative therapy, clinical efficacy and the improved toxicity profile compared with current available treatments
- Believes the ibrutinib should be available for patients with relapsed and refractory Waldenström's to address a significant unmet clinical need

Specific issues

- ***Overall survival assumptions*** – Clinical opinion, based on evidence presented, that ibrutinib will provide a significant survival benefit
- Reasonable to assume pre-progression survival may be better in ibrutinib group due to greater haematological and infectious complications resulting from chemotherapy (particularly in the relapsed/ refractory) setting

Clinical expert 2 comments

Cancer Drugs Fund

- Final decision on the CDF should be made when the modelling and pricing issues have been resolved
- Additional data from PCYC-1118E and iNNOVATE will be available within 2 years (including treatment-naïve patients)
- Progression free and overall survival data are unlikely to become available within 2 years of CDF, response data would be valuable.
- Registry provides an excellent opportunity to collect real world response data

Equality issues

- WM is a disease of older people and more common in men

Naive population

- Agrees that there is currently no evidence to support the use of ibrutinib in treatment naïve patients.

Key decisions

- Can the committee accept an ICER of £54,000 per QALY gained?
  - £20-30,000 per QALY is the usual range of cost effectiveness (*NICE Methods guide)*
  - What would be the grounds for doing so?
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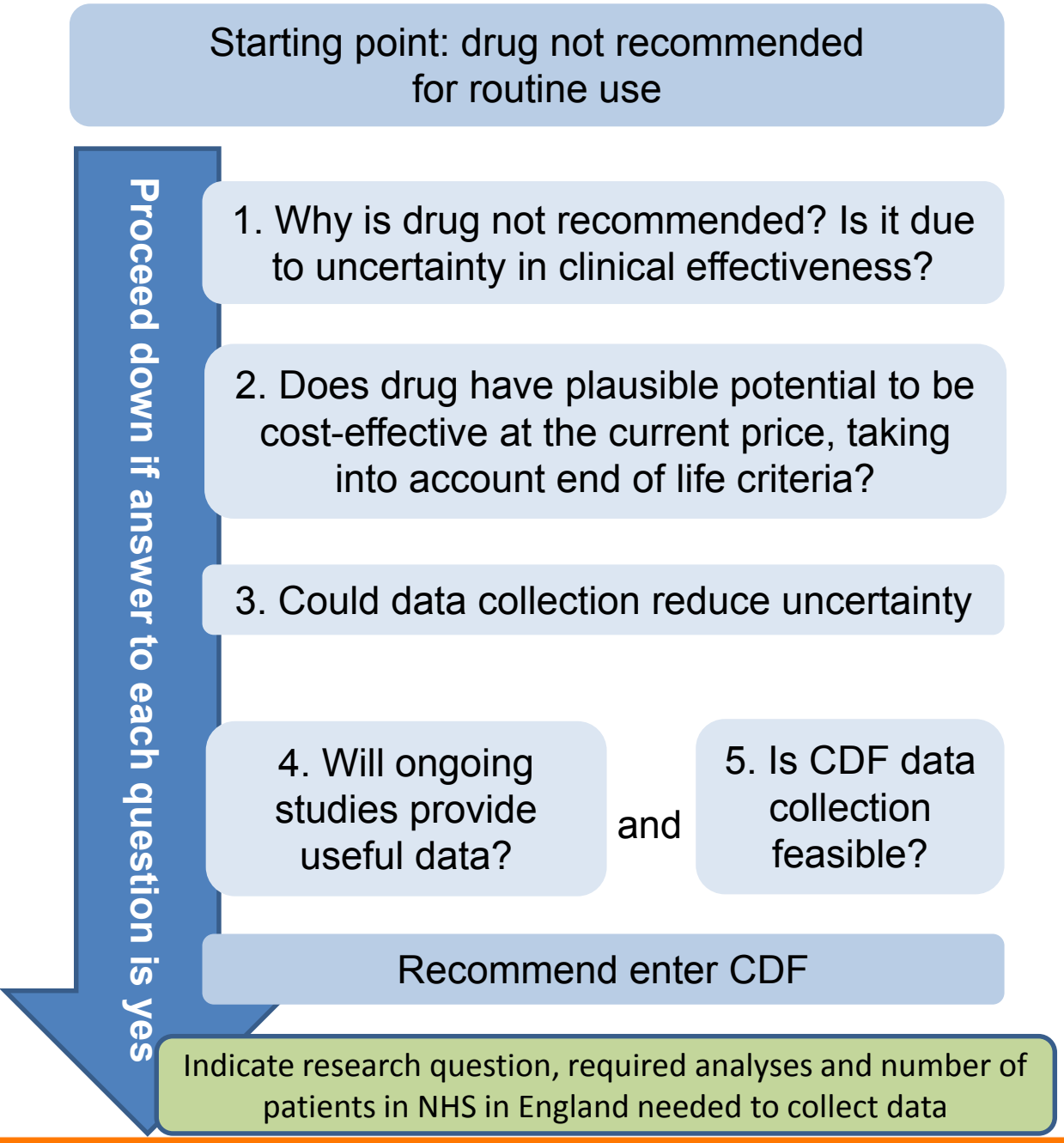
- Are there any innovative aspects of ibrutinib not captured by the QALY? If so, would their inclusion bring the ICER within a range that would be considered a cost effective use of NHS resources?
- Is ibrutinib for treating WM a suitable candidate for the Cancer Drugs Fund?

Cancer Drugs Fund criteria

The following criteria must be met:

- ICERs presented have the plausible potential for satisfying the criteria for routine use, taking into account the application of the End of Life criteria where appropriate.
- Clinical uncertainty can be addressed through collection of outcome data from patients treated in the NHS
- Data collected (including from research already underway) will be able to inform a subsequent update of the guidance.
  - This will normally happen within 24 months



Guidance for appraisal committees:

When should NICE recommend that a product enters the CDF?