Proactive therapeutic drug monitoring of biologic drugs in adult patients with inflammatory bowel disease, inflammatory arthritis, or psoriasis : a clinical practice guideline

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Additional material is published online only. To view please visit the journal online

Cite this as: *BMJ* 2024;387:e079830
http://doi.org/10.1136/bmj-2024-079830

RAPID RECOMMENDATIONS

Proactive therapeutic drug monitoring of biologic drugs in adult patients with inflammatory bowel disease, inflammatory arthritis, or psoriasis: a clinical practice guideline

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ABSTRACT

CLINICAL QUESTION

In adult patients with inflammatory bowel disease, inflammatory arthritis (rheumatoid arthritis, spondyloarthritis, psoriatic arthritis), or psoriasis taking biologic drugs, does proactive therapeutic drug monitoring (TDM) improve outcomes as compared with standard care?

CONTEXT AND CURRENT PRACTICE

Standard care for immune mediated inflammatory diseases includes prescribing biologic drugs at pre-determined doses. Dosing may be adjusted reactively, for example with increased disease activity. In proactive TDM, serum drug levels and anti-drug antibodies are measured irrespective of disease activity, and the drug dosing is adjusted to achieve target serum drug levels, usually within pre-specified therapeutic ranges. The role of proactive TDM in clinical practice remains unclear, with conflicting guideline recommendations and emerging evidence from randomised controlled trials.

THE EVIDENCE

Linked systematic review and pairwise meta-analysis which identified 10 trials including 2383 participants. Inflammatory bowel disease, inflammatory arthritis, and psoriasis were grouped together as best current research evidence on proactive TDM did not suggest heterogeneity of effects on outcomes of interest. Proactive TDM of intravenous infliximab during maintenance treatment may increase the proportion of patients who experience sustained disease control or sustained remission without considerable additional harm. For adalimumab, it remains unclear if proactive TDM during maintenance treatment has an effect on sustained disease control or sustained remission. At induction (start) of treatment, proactive TDM of intravenous infliximab may have little or no effect on achieving remission. No eligible trial evidence was available for proactive TDM of adalimumab at induction (start) of treatment. No eligible trial evidence was available for proactive TDM of other biologic drugs in maintenance or at induction (start) of treatment.

RECOMMENDATIONS

The guideline panel issued the following recommendations for patients with inflammatory bowel disease, inflammatory arthritis, or psoriasis:

1. A weak recommendation in favour of proactive TDM for intravenous infliximab during maintenance treatment
2. A weak recommendation against proactive TDM for adalimumab and other biologic drugs during maintenance treatment
3. A weak recommendation against proactive TDM for intravenous infliximab, adalimumab, and other biologic drugs during induction (start) of treatment.

UNDERSTANDING THE RECOMMENDATIONS

When considering proactive TDM, clinicians and patients should engage in shared decision making to ensure patients make choices that reflect their values and preferences. The availability of laboratory assays to implement proactive TDM should also be considered. Further research is warranted and may alter recommendations in the future.

HOW THIS GUIDELINE WAS CREATED

An international panel including patient partners, clinicians, and methodologists produced these recommendations based on a linked systematic review and pairwise meta-analysis which identified 10 trials including 2383 participants. The panel followed standards for trustworthy guidelines and used the GRADE approach, explicitly considering the balance of benefits and harms and burdens of treatment from an individual patient perspective.

Why is the guideline needed?

Inflammatory bowel disease, inflammatory arthritis (rheumatoid arthritis, spondyloarthritis, and psoriatic arthritis), and psoriasis are chronic immune mediated inflammatory diseases with a high burden on patients' health, quality of life, and use of healthcare

This *BMJ* Rapid Recommendations article is one of a series that provides clinicians with trustworthy recommendations for potentially practice changing evidence. *BMJ* Rapid Recommendations represent a collaborative effort between the MAGIC group (www.magicproject.org) and *The BMJ*. A summary is offered here, and the full version including decision aids is on the MAGICapp (www.magicapp.org), for all devices in multilayered formats. Those reading and using these recommendations should consider individual patient circumstances and their values and preferences and may want to use consultation decision aids in MAGICapp to facilitate shared decision making with patients. We encourage adaptation of recommendations to allow contextualisation of recommendations and to reduce duplication of work. Those

resources.[1-7] Emerging treatment options for these conditions have improved patient outcomes over the past two decades, especially after the introduction of biologic drugs such as tumour necrosis factor inhibitors (TNFi).[3 6 8-10] Biologic drugs are used by a substantial proportion of patient populations worldwide, with usage varying with disease and geographical location.[11-16]

Despite these advances, some patients do not reach disease remission and/or disease control.[3-5 7] Biologic drugs are usually dosed according to body mass and/or fixed dosing to all patients, and large variations in patient serum drug levels are seen even among patients on the same dose. For several of these drugs (including infliximab and adalimumab), higher serum drug levels are associated with treatment effectiveness.[17 18] A proportion of patients develop anti-drug antibodies, which can block the action of the drug and increase drug clearance, reducing the effectiveness of the treatment.[19-22]

Therapeutic drug monitoring (TDM) of biologic drugs is being investigated as a method to optimise treatment to improve effectiveness and reduce side effects.[23] TDM may be proactive or reactive. Proactive TDM is the measurement of drug concentrations and anti-drug antibodies at timed intervals irrespective of disease control. Reactive TDM is the measurement of drug concentrations and anti-drug antibodies triggered by a clinical event (a disease flare, for example). Both proactive and reactive TDM aim to optimise individual patient dosage regimens and therefore improve outcomes. Proactive TDM has the additional aim of preventing disease flares.[24] With proactive TDM, individual patient drug doses are adjusted based on the results of periodic measurements to avoid patients falling outside the target serum drug levels.[17] Practical information on serum drug and anti-drug antibody measurements can be found on MAGICapp: https://app.magicapp.org/#/guideline/7735/section/146829.

Despite randomised controlled trials (RCTs) showing promising results with proactive TDM of biologic drugs, current guideline recommendations diverge concerning whether to use this novel approach, when to use it, and for what diseases.[6 10 17 20 24-27] Surveys among US, UK, Indian, and Scandinavian gastroenterologists show that proactive TDM of TNFi has been variably adopted in clinical practice (20-60%), reflecting the diverging guidelines.[28-31] We have not identified any guideline applying appropriate standards and methods that includes the most recent trial evidence. Our guideline was triggered by a RCT investigating the use of proactive TDM in the maintenance treatment of inflammatory arthritis, inflammatory bowel disease, and psoriasis with intravenous infliximab.[24] This trial reported a benefit with proactive TDM across inflammatory bowel disease and inflammatory arthritis, with no associated harm.

About this guideline

This guideline contributes to the BMJ Rapid Recommendations series—a collaborative effort between MAGIC Evidence Ecosystem Foundation and *TheBMJ*—which is focused on providing clinicians with trustworthy recommendations for potentially practice changing evidence. Box 1 gives linked resources for this guideline, including a systematic review and meta-analysis evaluating proactive TDM of biologic drugs in immune-mediated inflammatory diseases.[32] This systematic review synthesised findings from 10 randomised controlled trials, with a total of 2383 patients.[32]

Box 1: Linked resources in these BMJ Rapid Recommendations

- Kawano-Dourado L, Kristianslund EK, Zeraatkar D, et al. Proactive therapeutic drug monitoring of biologic drugs in adult patients with inflammatory bowel disease, inflammatory arthritis, or psoriasis: a clinical practice guideline. *BMJ* 2024;386:e079830.
- Zeraatkar D, Pitre T, Kirsh S, et al. Proactive therapeutic drug monitoring of biologic drugs inpatients with inflammatory bowel disease, inflammatory arthritis, and psoriasis: systematic review and meta-analysis. *BMJMED* 2024;3:e000998.
- MAGICapp. An expanded version of the guideline with multi-layered recommendations, evidence summaries, and decision aids for use on all electronic devices. https://app.magicapp.org/#/guideline/nBAezL.

An international panel that included patients, healthcare professionals, and methodologists created these recommendations following globally accepted standards for trustworthy guidelines and using the GRADE approach.[33] No panel member reported financial conflicts of interest. Intellectual and professional conflicts were minimised and managed. For more information on how this guideline was created please see MAGICapp (https://app.magicapp.org/#/guideline/nBAezL). Briefly, the recommendations synthesise the best available evidence on benefits and harms, the expertise and experience of the guideline panel (which also included patient representatives), and what we understood about the values and preferences of patients living with inflammatory bowel disease, inflammatory arthritis, or psoriasis.

The recommendations also take into account practical issues, geographical variation in practice, implementability, and patient burden. The recommendations do not explicitly take into account cost effectiveness or other healthcare system factors as we take an individual patient perspective.

The Recommendations

Recommendation 1: For adult patients with inflammatory bowel disease, inflammatory arthritis, or psoriasis receiving treatment (maintenance) with intravenous infliximab we suggest proactive TDM rather than reactive TDM or no TDM

Go to MAGIC app to read more (https://app.magicapp.org/#/guideline/nBAezL)

Understanding the recommendation

When making a weak recommendation for the use of TDM in patients taking intravenous infliximab as maintenance treatment, we recognised the potentially important benefit of an absolute 14% rate increase (ranging from 8% to 22% increase) in sustained disease remission and/or disease control as compared with standard care (no TDM or reactive TDM) with no evidence of harm. We assumed that most patients would value proactive TDM if it increased sustained disease control and/or sustained remission by 5% without causing additional serious harm. As the lower bound of the 95% confidence interval is 8%, we considered it a significant benefit compared with standard care.

Nevertheless, the anticipated benefits and harms were informed by low to very low certainty evidence from four RCTs with a total of 872 patients identified in the systematic review.[32] This uncertainty precluded us from making a strong recommendation for the use of TDM in these patients. The low certainty evidence rating stemmed

from the risk of bias in the RCTs (owing to lack of blinding), indirectness in the body of evidence owing to grouping different diseases together (box 2) and limited follow-up of patients.

Box 2: Key points to check before reading the recommendations

Different diseases grouped together, separate recommendations for different drugs

Inflammatory bowel disease, inflammatory arthritis, and psoriasis were grouped together after careful guideline panel discussions. This decision was supported by a systematic review that did not suggest subgroup effects on the outcomes of interest.[34] In such situations of uncertainty (subgroup effects may still exist as the evidence is limited in completely ruling it out), GRADE recommends grouping diseases (populations) under the same recommendation while assessing potential subgroup effects.[34] On the other hand, recommendations for different drugs were segregated because of known differences between drugs that affect the effect of proactive TDM. For example, there may be increased immunogenicity with intravenous, chimeric drugs such as intravenous infliximab compared with subcutaneous fully human protein drugs such as adalimumab, which may influence the effectiveness of proactive TDM. For more detailed reasoning, see the methodology section in MAGICapp (https://app.magicapp.org/#/guideline/8158/section/174611).

Who does this guideline apply to?

The recommendations apply to adult patients (aged 18 and older) with inflammatory bowel disease, inflammatory arthritis, or psoriasis. In this guideline, inflammatory arthritis refers to rheumatoid arthritis, spondyloarthritis, and psoriatic arthritis.[20]

What is proactive TDM?

TDM is the practice of measuring serum drug levels and anti-drug antibodies, adjusting the drug dose to achieve target serum drug levels, usually within a predefined therapeutic range.[17] The therapeutic range may be general, population specific, or specific to the individual patient.[35] Also included in the concept is the change in biological drug for high levels of anti-drug antibodies.[19] TDM can be proactive or reactive. In proactive TDM, the drug dosing is regularly adjusted based on drug serum levels that are measured at predefined intervals, irrespective of whether patients display symptoms or signs of clinical deterioration. In contrast, in reactive TDM, serum drug levels and anti-drug antibodies are only measured in response to disease worsening, non-response to treatment, or occurrence of an adverse event. Despite wide global variation in practice, reactive TDM is much more commonly used than proactive TDM and increasingly represents standard care.[28-31]

During what phases of treatment is proactive TDM applied?

Induction (start) of treatment—Biologic drugs are typically started when patients are in a state of active disease, and the aim of treatment during the first phase is to achieve disease control, preferably by reaching a state of remission.

Maintenance treatment—In this scenario, patients have achieved disease control and the aim is to avoid disease worsening.

Management approach to maintenance and induction treatment may vary by disease type. For example, for adalimumab in inflammatory arthritis, the same drug dose is given at the start of treatment and during maintenance, while for inflammatory bowel disease a higher dose is given at the start of treatment.

What is the difference between sustained disease control, sustained remission, and remission?

Different outcomes have been used in different clinical trials to measure the degree of disease control in maintenance treatment. Sustained disease control and sustained remission may sound similar, however, they reflect different measurements. Sustained disease control was defined as not having a significant increase in disease activity at any point during the study period. Sustained remission was defined as disease activity consistently below a predefined threshold throughout the study period. Sustained disease control and/or sustained remission were prioritised as critical outcomes and were combined into a single outcome for recommendations 1 and 2.

For the induction scenario (recommendation 3), remission was prioritised as a critical outcome. It refers to the proportion of patients in remission at the time the outcome was measured. For additional details on outcomes, see MAGICapp, "How this guideline was made" (https://app.magicapp.org/#/guideline/8158/section/174610).

Which patients would benefit most?

When considering implementing proactive TDM, clinicians should consider individual characteristics associated with worse prognosis, such as high baseline disease activity, high risk of non-adherence, previous loss of treatment effect, obesity, lack of immunosuppressive co-medication, and, for the particular case of patients with inflammatory bowel disease, persistently elevated faecal calprotectin.[36]

Access to serum drug level measurements and anti-drug antibody testing

To implement proactive TDM, access to drug level and anti-drug antibody measurements is needed. See the section "Implement and adapt the guideline" in MAGICapp for more details (https://app.magicapp.org/#/guideline/8158/section/174606).

Finally, a key element leading to a weak (instead of a strong) recommendation was the concern about the influence of disease specific factors such as a lower risk of flare consequences in psoriasis and inflammatory arthritis, and a higher risk of flare consequences in inflammatory bowel disease (need of hospital admission, surgical intervention).

Recommendation 2: For adult patients with inflammatory bowel disease, inflammatory arthritis, or psoriasis receiving treatment (maintenance) with adalimumab or other biologic drugs we suggest not using proactive TDM

Go to MAGIC app to read more (https://app.magicapp.org/#/guideline/nBAezL)

Understanding the recommendation

In agreeing on a weak recommendation against the use of adalimumab, we were mostly concerned about the very low certainty evidence for use of proactive TDM during maintenance treatment: the only evidence available informing critical outcomes (sustained remission and/or sustained disease control) was a small trial with 78 children and adolescents, a group outside the scope of this guidance.[37] A larger body of evidence (three studies, 633 patients) was available for the outcome remission (measured at the end of the follow-up period) but this estimate was imprecise, ranging from a reduction of 9% remission events to an increase of 30% in absolute terms. The very low certainty of the evidence combined with our decision to place a high value on avoiding patient burden of potential extra clinic visits for blood sampling (as adalimumab is most often self-administered subcutaneously at home), resulted in a weak recommendation against proactive TDM for adalimumab, while waiting for better trial evidence to become available (https://en.remedy-senter.no/project/ra-drum).

For other biologic drugs, no trial evidence was available for proactive TDM, leading to a weak recommendation against proactive TDM with other biologics.[32] A strong recommendation against proactive TDM during maintenance treatment with adalimumab or other biologic drugs was deemed inappropriate given the uncertainty in the evidence added to the biological plausibility of a possible beneficial effect, especially for adalimumab. In this context, on a case-by-case basis, depending on values or preferences (ie, higher value placed on avoiding disease flares), some patients—such as those at highest risk of disease flares with major consequences—may prefer to receive the intervention.

A "weak recommendation against" may still offer room for the use of proactive TDM on an individual basis. In general, patients at the

highest risk of disease flares will benefit most from proactive TDM (box 2).

Recommendation 3: For adult patients with inflammatory bowel disease, inflammatory arthritis, or psoriasis starting treatment with intravenous infliximab, adalimumab, and other biologic drugs we suggest not using proactive TDM

Go to MAGIC app to read more (https://app.magicapp.org/#/guideline/nBAezL)

Understanding the recommendation

The weak recommendation against proactive TDM of intravenous infliximab at the start of treatment (induction scenario) is supported by the lack of benefit observed in one study with 398 patients.[38] The effect of proactive TDM of intravenous infliximab could vary from a reduction of 8% remission events to an increase of 11% in absolute terms. Additionally, the certainty of the evidence was very low owing to the risk of bias, imprecision, and indirectness. We felt it inappropriate to extrapolate indirect evidence from maintenance to the induction (start of treatment) scenario given the differences in the induction scenario (when patients are experiencing a flare), and drug dosing may be greater than during maintenance treatment thus limiting the effect of dose adjustments and reducing the risk of generating anti-drug antibodies. This reduces the benefit of proactive TDM.[19]

The weak recommendation against proactive TDM for induction with adalimumab and other biologics was because of the lack of eligible evidence (RCTs). In the absence of evidence, we agreed that most well informed patients would prefer not to have the intervention. We also judged it inappropriate to extrapolate data on intravenous infliximab to adalimumab and to other biologics. Infliximab is expected to be more immunogenic than other biologics, which increases the risk of anti-drug antibodies and consequently the benefit from proactive TDM. Patient burden is also different between infliximab, which is given intravenously, and adalimumab, which is self-administered subcutaneously.

Uncertainties

Little robust research evidence is available on proactive TDM, apart from the maintenance treatment with intravenous infliximab. This led to weak recommendations against proactive TDM for drugs other than intravenous infliximab during maintenance treatment and for all drugs at the start of treatment (induction) scenario.

Limited research evidence also prevented the proper investigation of subgroup effects, especially related to different biologic drugs and different diseases. Although we did not find evidence that the effect of proactive TDM was different between disease groups or between studies with high and low risk of bias, not enough data were available that we could confidently exclude it. We anticipate the need for updates and revisions of these guidelines as new data emerge. If new evidence emerges that suggests different outcomes between disease groups, the guideline panel may need to reconsider whether separate recommendations are needed for individual diseases.

The length of follow-up (maximum of 68 weeks [44 to 68 weeks]) is another critical limitation of the available evidence. Like patients, healthcare providers and policy makers are interested in long term effects of the intervention, and the lack of direct evidence on outcomes measured after longer follow-up times adds uncertainty to decisions aiming at long term disease control and/or disease remission.

Data on patient values and preferences are lacking; no systematic review or survey was conducted on the topic. However, we agreed that most well informed patients would be willing to use an intervention for which there is evidence of benefit in critical outcomes without significant accompanying harms.

The costs of proactive TDM were not analysed or factored in these guidelines, nor were equity issues related to its implementation. These elements should be integrated into the decision to implement proactive TDM at the regional level.

Lack of a gold standard for the assay to measure drug levels and anti-drug antibodies is another source of uncertainty. The measurement of serum drug concentrations and, especially, anti-drug antibodies, comes with technological and practical challenges. This includes variation in measurements between different assays, especially for measurements of anti-drug antibodies. Because of the associated complexities, the World Health Organization advises that serum drug levels and anti-drug antibodies measurements may only be performed in experienced laboratories with the prerequisite expertise to provide informed interpretation of the data generated.[39] More information on measurement methods can be found on MAGICapp (https://app.magicapp.org/#/guideline/8690/section/187577).

Implementation and adaptation of the guideline

To implement the weak recommendation in favour of proactive TDM for patients on maintenance treatment with intravenous infliximab, decision makers should consider a range of factors. We have identified some key implementation facilitators and barriers through published studies, semi-structured interviews with clinical experts, and panel discussions.[28-31 35] Before implementing the recommendations, we suggest you go to MAGICapp (https://app.magicapp.org/#/guideline/8690/rec/174043) to see what you need to:

- Know (eg, access to validated assays, frequency)
- Consider (eg, are the costs acceptable in your setting?)
- Decide on (eg, the algorithm to use for dosing proactive TDM)
- Do (eg, educate clinicians and inform patients).

Of note, little evidence is available on how often proactive TDM should be done to be beneficial. Both the Nor-drum trial and the Taxit trial took blood samples before every infusion for one year.[24 40] We recognise that the frequency of the proactive TDM would need to depend on local context and capacity. On MAGICapp (https://app.magicapp.org/#/guideline/8690/rec/174043), in the section on practical information on recommendation 1, a suggested algorithm for proactive TDM can be found.

One important point to consider in the implementation of proactive TDM relates to the assays for the measurement of serum drug levels and anti-drug antibodies. Different assays for the measurement of serum drug levels usually show a good correlation, and some guidance exists regarding therapeutic thresholds for serum drug levels.[17] The same assay should be used when following individual patients over time to ensure comparability between measurements.[17-19] The measurement of anti-drug antibodies is often performed only when drug serum levels are low, aiming at investigating if anti-drug antibodies are the cause of low serum drug levels. Many different strategies are used for the measurement of anti-drug antibodies providing data that can be difficult to interpret.[19] Particular consideration should be given to whether the assay only measures neutralising anti-drug antibodies (blocking

the effect of the drug), or whether the assay also measures non-neutralising anti-drug antibodies, as well as whether the assay measures anti-drug antibodies in the presence or absence of drug.

This guideline takes an individual patient perspective, and national or local guidelines may modify recommendations, based on the same evidence on benefits and harms. Beyond perceived differences in patients' values and preferences, several factors may influence decision making in terms of the healthcare system.[41] For example, specific elements of the weak recommendation supporting proactive TDM for intravenous infliximab on maintenance treatment may not universally apply because of factors such as limited laboratory access, out-of-pocket costs, or the need to maintain laboratory capacity for groups with a higher burden of disease. Given the uncertainty in the existing evidence, we recommend exercising caution when making strong recommendations in local guidelines until more compelling evidence is available.

How patients were involved in the creation of this article

Our panel included two patients living with inflammatory bowel disease and inflammatory arthritis. Their perspectives helped the panel to consider better the values and preferences associated with decision making related to proactive TDM of biologic drugs.

Our patient partners have contributed in various ways, including but not limited to: collaborating in the identification of priority areas, drawing from their own experiences and those of the broader patient community; participating in guideline development meetings, where their perspectives were integral in crafting recommendations that resonate with the needs and preferences of patients; reviewing draft versions of the guideline, offering feedback from a patient's viewpoint to enhance clarity, accessibility, and relevance; and validating the final recommendations to ensure they are truly reflective of patient values, preferences, and experiences.

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Funding: Centre for Treatment of Rheumatic and Musculoskeletal Diseases (REMEDY) is funded as a Centre for Clinical Treatment Research by the Research Council of Norway (project 328657). Center for Molecular Prediction of Inflammatory Bowel Disease (PREDICT) is a Center of Excellence funded by the Danish National Research Foundation (DNRF148). MAGIC has provided methodological contributions and support throughout the guideline process. The project has received funding from the European Union's Horizon Europe research and innovation programme under grant agreement number 101095052.

Competing interests: All authors have completed the *BMJ* Rapid Recommendations interest of disclosure form. MAGIC and *The BMJ* judged that no panel member or co-chair had any financial conflict of interest. Professional and academic interests are minimised as much as possible, while maintaining necessary expertise on the panel to make fully informed decisions. MAGIC and *TheBMJ* assessed declared interests from other coauthors of this publication and found no relevant conflicts of interests.

Provenance and peer review: This publication was commissioned by *The BMJ* in partnership with the MAGIC Evidence Ecosystem Foundation, in the context of the *BMJ* Rapid Recommendations. Pre-publication internal and external peer review was managed by MAGIC, and internal review was managed by *The BMJ*. Post-publication review through rapid responses is facilitated on bmj.com and through MAGICapp.

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Main infographic: Summary of recommendations and evidence

Visual summary of recommendation

Population

These recommendations apply only to people with these characteristics:

Adults with immune-mediated inflammatory diseases

Being treated with or starting treatment with infliximab, adalimumab, or other biologic drugs

- Inflammatory bowel disease
- Inflammatory arthritis
  - Rheumatoid arthritis
  - Spondyloarthritis
  - Psoriatic arthritis
- Psoriasis

May or may not apply to: ? Other immune-mediated inflammatory diseases

Does not apply to: ✖ Inflammatory diseases that are not immune-mediated

See an interactive version of this graphic online

https://bit.ly/bmj-rr-bio

Recommendations

1

Standard care (Reactive or no monitoring)		or	Proactive monitoring	
Strong	Weak		Weak	Strong

Adults receiving maintenance therapy with infliximab

"We suggest proactive therapeutic drug monitoring"

2

Standard care (Reactive or no monitoring)		or	Proactive monitoring	
Strong	**Weak**		Weak	Strong

Adults receiving maintenance therapy with adalimumab and other biologics

"We suggest not using proactive therapeutic drug monitoring"

3

Standard care (Reactive or no monitoring)		or	Proactive monitoring	
Strong	**Weak**		Weak	Strong

Adults starting therapy with infliximab, adalimumab, and other biologics

"We suggest not using proactive therapeutic drug monitoring"

Key practical issues

Recommendation 1

- Requires access to laboratory with validated analyses of infliximab serum drug levels and anti-drug antibodies
- Drug dosing is adjusted to keep serum drug levels in a defined therapeutic range, typically by using an algorithm
- There is little evidence on how often proactive monitoring should be done to be beneficial

Recommendations 2 and 3

- Proactive therapeutic drug monitoring involves regularly measuring serum drug levels and anti-drug antibodies

Values and preferences

There was no evidence about how individuals with an immune mediated inflammatory disease would judge the success of proactive monitoring.

Recommendation 1

An assumption was made that most patients would value proactive monitoring if it increased sustained disease control, sustained remission, or both by 5% without causing additional serious harm

Recommendations 2 and 3

An assumption was made that most patients would prefer standard care, given the very low certainty of the evidence informing this recommendation