Protocol for a rapid review of
New drug treatments for juvenile idiopathic arthritis: Etanercept and Infliximab

Commissioned by the HTA programme on behalf of NICE

A. Details of review team

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B. Title of research question

What is the clinical effectiveness and cost effectiveness of the anti tumour necrosis factor agents ~~(including~~ etanercept (Enbrel™) ~~and infliximab)~~ in juvenile idiopathic arthritis patients?

C. Clarification of research question and scope

Description of technology and indications

Both juvenile idiopathic arthritis (JIA) and rheumatoid arthritis (RA) are diseases which involve in the immune system. Understanding of the role of the natural (or innate) immune system, (the host defence mechanisms involving neutrophils, monocytes, macrophages and natural killer cells as opposed to the adaptive or acquired immunity (production of specific antibodies or cells in response to foreign agents), and of the protein mediators produced in its activation (cytokines), in the inflammatory processes of rheumatoid disease has advanced sufficiently to allow the development of therapeutic agents that target these pathological immune responses.[1-3] The first of these new biologic agents to be licensed for human use are anti-Tumour Necrosis Factor-alpha (aTNF-α) agents.

The TNF cytokine family first attracted attention because of its involvement in programmed cell death (apoptosis), but TNF is also involved in the inflammatory process and possibly in the joint destruction found in rheumatic disease. Many cytokines are present in the synovial compartment in rheumatic disease, both pro-inflammatory, including TNF-α and Interleukin-1 (IL-1), and anti-inflammatory, including IL-10 and TGFβ, but with a net inflammatory effect. The types and quantities of serum cytokines and soluble cytokine receptors found in JIA varies according to JIA subtype [2]. TNF-α is a regulator of IL-1, a pro-inflammatory cytokine in turn involved the regulation of other pro-inflammatory cytokines. Both have been implicated in joint inflammation and destruction as they induce the synthesis and release of metalloproteinases, prostaglandins and nitric oxide within cells[1]. Agents that inhibit the action of TNF-α or of IL-1 thus might be expected to have the potential to modify the inflammatory processes of rheumatic disease[3].

Two TNF-α inhibitors are currently licensed for use in the UK, etanercept (Enbrel™) and infliximab (Remicade™). Etanercept is soluble TNF-α receptor and is a "designer molecule" consisting of two of the normal receptors for TNF (extra-cellular p75 ligand) and a portion of a human immunoglobulin protein (Fc portion of IgG1). It is administered as a twice-weekly sub-cutaneous injection and may be, and in clinical practice is expected to be, given for an indefinite period. It works by competitively binding to TNF-α, thus preventing it from binding to cellular receptors. It also binds to Interleukin-1-α, known to be active in JIA [4]. Infliximab is a chimeric monoclonal antibody that binds soluble and cell-attached TNF-α, inhibiting TNF-α activity. Infliximab is given as periodic intravenous infusions, but is not currently licensed for use in children in the UK. Adult patients with rheumatoid arthritis who are treated relatively frequently with infliximab must also be treated with

methotrexate. This reduces the risk of formation of antibodies against the drug and thus the risk of allergic reactions. Etanercept can be administered alone.

Etanercept is currently licensed for juvenile idiopathic arthritis in children who have not responded to or are intolerant of methotrexate.[5] Such children are most likely to have a diagnosis of extended oligoarthritis, polyarticular arthritis or systemic arthritis and will have developed or will be at risk of developing functional disabilities and damage to joints. Further biologic agents targeting cytokines or inflammatory cells are likely to come into clinical use in the next few years and would raise similar questions over short and long term outcomes and safety to those that arise with etanercept, the first licensed agent.

Epidemiology and current service provision

Juvenile idiopathic arthritis (JIA) (usually known as juvenile rheumatoid arthritis (JRA) in the USA) comprises a heterogeneous group of painful conditions involving persistent swelling of the joints with variable presentation and course, with approximately 20% developing destructive joint disease[2;6] (Table 1). Young children, however, may not complain of pain at presentation and detection of swelling may require close examination, and non-specific symptoms such as lethargy and irritability are common[7]. Growth retardation may be a feature of severe JIA. The current, but still unvalidated[8], classification of JIA is the recently developed International League Against Rheumatism Taskforce (ILAR) classification (see Table 1)[6:9], but previously European (EULAR classification) and US (ACR classification) terminology had differed[10]. Caution should therefore be used in comparing studies using different classifications. The ILAR classification identifies clinically homogeneous groups, as knowledge of genetic and other factors is not yet adequate to arrive at a classification based on pathology.

The reported distribution of JIA subgroups varies from country to country, but in Europe and North America oligoarthritis accounts for more than half of the cases, with about a quarter having polyarthritis and about 10% having systemic disease[10].

Table 1: ILAR classification of JIA, disease characteristics and treatment[6;9]

Systemic arthritis	*Diagnosis*	*Characteristics*	*Typical prognosis*
	Spiking fever, transient rash, high ESR and C-reactive protein, –ve autoantibodies	Peak age onset 2 years, typically followed by polyarthritis, no HLA association	Polyarthritis progress, systemic features may regress over 3-4 years. ~~Untreated~~ Uncontrolled systemic disease can progress to amyloidosis with renal failure and ~~-~~high mortality
	Typical treatment		
	NSAIDs - High dose steroids - Methotrexate (for persistent polyarthritis, equivocal benefit for systemic features)~~equivocal benefit~~		
Oligoarthritis (persistent)	*Diagnosis*	*Characteristics*	*Typical prognosis*
	4 or fewer joints involved, usually wrists, knees, ankles	Mainly girls, peak age of onset 3, often localised and mild, associated with uveitis that may lead to visual impairment or blindness	Remission in 4-5 years
	Typical treatment		
	NSAIDS – Intra-articular or other~~intravenous~~ steroids (may remove need for NSAIDs) - Physiotherapy		
Oligoarthritis (extended)	*Diagnosis*	*Characteristics*	*Typical prognosis*
	Often raised ESR, 4 or fewer joints, extending to more within first year	Mainly girls, peak age of onset 3, associated with uveitis, chronic disease	Chronic disease, risk of functional disabilities
	Typical treatment		
	NSAIDS - Intra-articular or other~~intravenous~~ steroids - Low dose methotrexate ~~(oral)~~ Resistant cases subcutaneous methotrexate at higher doses - Resistant cases other DMARDs		
Polyarticular arthritis	*Diagnosis*	*Characteristics*	*Typical prognosis*
	More than 4 joints involved at presentation	Most rheumatoid factor (RF) –ve	Poor, widespread joint destruction, often joint replacement as young adults
	Typical treatment		
	NSAIDs - Intra-articular or ~~i.v.~~ steroids - Oral steroids - Low dose methotrexate - Resistant cases subcutaneous methotrexate at higher doses - Resistant cases other DMARDs~~.~~		
Enthesitis arthritis	*Diagnosis*	*Characteristics*	*Typical prognosis*
	HLA B27 associated, RF –ve, ANA +ve, peripheral arthritis	Mainly boys, teen and pre-teen, uveitis,	Functional outcome usually good, some hip joint erosion, ~~some~~ many progress to spondylarthropathies
	Typical treatment		
	NSAIDs - Sulphalazine ~~-~~ Methotrexate		

Table 1 continued

Psoriatic arthritis	*Diagnosis*	*Characteristics*	*Typical prognosis*
	Inflammation of fingers, toes and polyarthritis, psoriasis in child or 1° degree relative	Psoriasis in child or relative	Can be highly erosive
	Typical treatment		
	Generally treated with methotrexate, but e~~E~~fficacy ~~of methotrexate~~ not established in childhood disease		
Unclassified	Includes patients with overlapping features		

One serious complication of JIA is chronic uveitis which can lead to visual impairment or blindness in up to 12% of children with JIA with the condition and can result in the development of cataracts and glaucoma. Thus children with JIA are screened for early signs. Uveitis is most common in oligoarthritis, with 30 percent developing uveitis over six years[11] and in antinuclear antibody (ANA) positive patients. Therapy is with NSAIDs, oral and topical steroids (which themselves carry a risk of ocular damage) and immune suppressants such as methotrexate and cyclosporin, but therapeutic options have not been evaluated in RCTs~~.~~[12] and there is a place for new treatments found to be of proven effectiveness.

Incidence

A wide range of estimates for the incidence of JIA is found in the literature.[10] Some of the difference is attributable to differences in disease definition and some to differences in case finding and the population covered. The most reliable information comes from studies with populations covering clearly defined geographic areas. One such Swedish study found a rate of 11 cases per 100,000 population per year[13], and a UK study found a similar rate of 10 cases per 100,000 population per year.[14] Both of these studies used the EULAR classification.

Prognosis

The prognosis of JIA varies with the subtype. Estimation of the proportions of patients with persistent disease is complicated by the lack of a consensus on the definition of remission, by the referral bias inherent in hospital based series, by the differences in the length of follow-up, and by potential problems with loss to follow-up. It is possible that the prognosis of the cohort of children currently being treated for JIA may be better than previous cohorts, if in fact methotrexate proves have a better impact on longer term outcomes than previous treatments, as no cohort of children with JIA has hitherto left paediatric services with as well controlled disease.

While ~~most~~ many children presenting with oligoarthritis will experience remission within 5 years, ~~around a third~~ as many as 50 percent progress to extended oligoarthritis by six years from diagnosis[11], with 35 percent developing joint erosions. Around one third to one half of children with polyarticular arthritis will have active arthritis persisting into adult life, and around one third of those presenting with systemic disease will develop severe polyarthritis[15]. Patients with JIA of any type, particularly those who are negative for rheumatoid factor (RF –ve), may need multiple soft tissue release operations and joint replacement. Amyloidosis is a dangerous complication of uncontrolled JIA of any type.

Pathogenesis

The causes of, and mechanisms through which, JIA develops remain unclear. An autoimmune origin for JIA is suggested by associations of subtypes with major histocompatibility complex (MHC) types, by the presence of autoantibodies in some patients and by the association of JIA with selective immune system deficiencies.[2;6;16] Subtypes show different genetic features, primarily involving MHC. In common with many other conditions with an autoimmune component, JIA does not show a Mendelian inheritance pattern and can be characterised as a complex genetic trait, as members of a patient's family have a very small increased risk of developing the disease. This risk might result from an increased disposition to autoimmunity[16]. Environmental factors are also involved, possibly a common infection, but studies have been inconclusive[6].

Nature of problem

Treatment of oligoarticular, polyarticular and systemic JIA involves progressively NSAIDS, intra-articular or intravenous steroids, methotrexate and, if no response is achieved, further so-called Disease Modifying Anti-Rheumatic Drugs (DMARDs). Progression to more extensive treatment depends upon the initial presentation and classification of the disease, and upon response to initial therapies.[6] Table 1 shows typical treatment options for different forms of JIA, but for any individual patient progression to more intensive treatment will depend upon the patient's response, and children intially presenting as any subtype may go on to have severe disease, intensive treatment and a poor prognosis. Figure 1 illustrates referral pathways and treatments likely to be offered in different settings. In the UK, the majority of children who develop severe JIA will ultimately be seen by consultant paediatric rheumatologists, the majority of whom work in tertiary specialist centres, some of which are able to offer shared care, and this is the setting in which etanercept treatment would be available. Patients will either have been referred directly by their general practitioners (currently only sporadically in at least some centres) or else via general paediatricians, orthopaedic surgeons or rheumatologists. Treatment of JIA is best provided by multidisciplinary team that will include physiotherapists, occupational therapists, nurses, psychologists and social work, with easy access to other paediatric subspecialties including ophthalmology and orthopaedic surgery[6;7].

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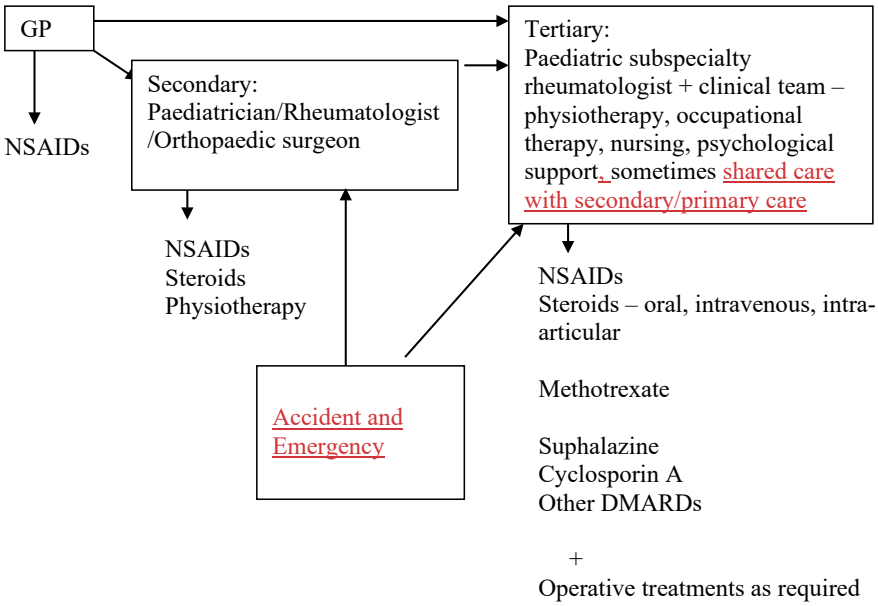
On initial presentation, unless systemic disease is present, patients are likely to be treated symptomatically with non-steroidal anti-inflammatory drugs (NSAIDs). Following referral, treatment with pulsed corticosteroids may follow where symptoms have not resolved, either oral or, for example, intravenous methylprednisolone (30mg/kg) over three days for polyarticular disease. Multiple intra-articular joint injections[17] are widely used, but as this treatment in children often requires general aneasthesia and theatre time, rapid treatment can present logistical problems, particularly in smaller centres. This treatment has not yet been evaluated in controlled clinical trials in children. A proportion of children, most commonly with oligoarthritis, will respond to steroids alone and will not require further treatment, but the outcome is poorer for children with multiple joint involvement.

Figure 1 Patient care path and treatment options in JIA



Children with systemic disease are likely to require more aggressive initial treatment, as they are sicker on initial presentation, and children without an adequate response to initial treatment will require further treatment. It is important to avoid long term treatment with corticosteroids in children wherever possible, as in addition to the problems caused by steroid dependency in people of all ages (including adrenal and immune suppression), steroid treatment in children can restrict growth.

There is no one treatment that universally controls the disease. Methotrexate is an immunosuppressant agent and low dose oral methotrexate (10 to 20 mg/m^2 [18;19] is now an established treatment for relatively severe and longstanding JIA, following a randomised control trial that established its efficacy compared with placebo over six months.[18] A further crossover placebo randomised control trial confirmed that it was effective over four months in treating extended oligoarthritis with equivocal results for systemic arthritis, two of the most disabling forms of the disease.[19] At the standard low dose, 60 to 70% of children might be expected to benefit. Higher doses

up to 25-30mg/m^2 administered subcutaneously are often used when there is no or only a partial response, and a trial organised by the Paediatric Rheumatology International Trials Organisation (PRINTO) is underway to establish whether higher does are more effective in children resistant to the low dose regimen.[20] Methotrexate may be an effective treatment of uveitis [21;22]. Methotrexate is of equivocal benefit in treating systemic features, but effective in treating other aspects of systemic disease. There is limited evidence on methotrexate's long term impact, but as magnetic resonance imaging has shown that joint damage occurs early in JIA and radiographic joint disease is a common early finding in children with JIA[20], there could be benefits in starting more aggressive treatment earlier in the course of the disease.[22]

While methotrexate is considered to be a relatively safe treatment when used in JIA, lymphomas have been reported in methotrexate treated patients including children and this may be a phenomenon related to rheumatic disease or a complication of treatment.[23] Although liver fibrosis and cirrhosis has been reported in adults following treatment with methotrexate, clinically significant fibrosis has not been reported in children[23] and treatment with the commonly used doses is considered to be safe. Haematological and liver enzyme monitoring necessitates regular blood tests during treatment. Methotrexate is a folinic acid suppressant, so folic acid is commonly prescribed with methotrexate. It is unclear how long methotrexate treatment needs to be continued if remission is achieved[20].

Methotrexate is one of several agents collectively known as disease-modifying anti-rheumatic drugs (DMARDs), but is now the drug of choice and most frequently used of these drugs in children with JIA.[20] These drugs, which include sulphasalazine, gold preparations, penicillamine, azathioprine, hydroxychloroquine, and cyclosporin A, act relatively slowly in comparison to corticosteroids, but may induce disease remission in adults with rheumatoid arthritis and reduce the risk of permanent structural joint damage. Most of these agents cause immune suppression in one way or another, although the mechanisms are not always fully understood. They have complex and different side effect profiles that complicate treatment. -The use of cyclosporin A, for example, has a high risk of renal complications. Results in children with JIA have often been disappointing with high rates of side effects.[24]

A few patients with very severe JIA where methotrexate treatment has not been successful have been treated with autologous bone marrow transplantation[25]. ~~Several~~ A high proportion of patients receiving transplants have died, however, and this treatment is not considered in routine clinical practice.

In summary, new treatments have been developed as a result of improved understanding of the immune system pathology in JIA, including aTNF agents. The effectiveness of the currently licensed agent, etanercept, and any further new interventions, needs to be evaluated in two areas.

- The treatment of children in whom methotrexate therapy does not succeed presents a challenge to clinicians. Typically this has involved agents which may have limited efficacy and substantial potential for adverse effects. Is the aTNF agent etanercept effective in the treatment of the relatively small number of JIA

patients who have not responded to, have not tolerated or have not complied with methotrexate treatment?

- Such patients are likely to have aggressive and relatively longstanding disease, and thus may already have structural joint damage. The question arises whether the aTNF agent etanercept and methotrexate have the potential to alter the course of disease: if they are of proven efficacy in the later stages of disease, could they also prevent structural damage and improve longer term outcomes, if used earlier in the course of disease?

These questions will arise with regard to any further new therapeutic agents for JIA.

The aims of this review are as follows:

- To provide a background review on juvenile idiopathic arthritis including epidemiology, current and emerging therapeutic options, and impact of disease on individuals and health services.
- To conduct a systematic review of the clinical benefits and hazards of the antiTNF agent etanercept in juvenile idiopathic arthritis compared with currently available treatments.
- To review the economic evidence and consider the economic, and clinical, advantages and disadvantages of using these agents compared with other treatment options.

D. Report Methods

Search Strategy

Medline (Ovid), Embase (Ovid), the Science Citation Index, and the Cochrane Library will be searched using MeSH subject headings (arthritis, juvenile rheumatoid) and keywords which encompass juvenile idiopathic arthritis ("juvenile idiopathic arthritis", "juvenile ~~chronic~~ rheumatoid arthritis" and "juvenile chronic arthritis"), tumor necrosis factor, tumor necrosis factor receptors, anti-TNF, quality of life, etanercept and infliximab. Data will also be sought in abstracts from relevant rheumatology and paediatric rheumatology meetings. Manufacturer and sponsor submissions to the National Institute for Clinical Excellence will be reviewed in detail. Safety data available on regulatory authority websites will be reviewed.

Systematic reviews and randomised control trials of DMARDs will be sought in order to inform the economic analysis and provide a context for biological anti-TNF therapies. The search strategies will be based on that developed by the Aggressive Research Intelligence Facility (ARIF; available on request) and by the Centre for Reviews and Dissemination. Reviews will be sought in Clinical Evidence, Medline, Bandolier, health technology assessment databases, in-house databases and the Cochrane Library.

Searches for relevant health economic analyses will be conducted.

Inclusion & Exclusion criteria

In order to assess clinical effectiveness, all randomised controlled trials of etanercept or infliximab versus any agent (including placebo) in juvenile idiopathic arthritis (including disease described as juvenile chronic arthritis) and in other rheumatic diseases of childhood will be considered. The patient population should be aged 18 or under, as the age at which young people transfer to adult services varies according to the practice current in particular treatment centres. Studies of unlicensed biological therapies targeted against TNF will be identified and described but not included in any meta-analysis. Studies reporting entirely on laboratory measures aimed at investigating disease or treatment mechanisms will not be included unless relevant clinical outcomes, that are not described elsewhere, are provided.

Data extraction strategy

Data will be extracted independently by two reviewers. Discussion or involvement of a third reviewer will be used to resolve discrepancies. One reviewer will screen foreign language publications using English abstracts if available. Translations will be obtained where necessary.

Data extraction will focus on clinical outcomes, including the standard definition response in terms of changes to the Core Outcome Variables, but will include accepted radiographic outcomes if available. Outcomes in JIA in both clinical practice and research are now commonly measured by a core set of six outcome variables, physician's global impression, parent/patient global impression, number of active joints, number of joints with limited range of motion, functional ability and ESR. An improvement of at least 30 percent in at least three of these, and a deterioration of more than 30 percent in no more than one variable constitutes a validated endpoint for improvement.[26] But as this endpoint was validated on mainly polyarticular patients, it may be a less appropriate endpoint for other subgroups. For example, coevaluation of uveitis in cases with single joint involvement might be appropriate.[26] Research which pre-dates this consensus on outcomes is likely to measure similar outcomes, but may not use the same definition of response.

Health related quality of life measures will be included if available, as will other outcomes relevant to the quality of life of children and young people, for example days off school. The characteristics of patients included in studies will be sought in detail in order to allow comparisons between studies and to judge relevance to routine care.

For many patients, JIA is a chronic disease that requires long-term treatment. Immediate response, medium-term and long-term outcomes will therefore all be considered.

Quality assessment strategy

The quality of identified RCTs will be examined by using a validated quality assessment checklist such as that developed by Jadad and colleagues.[27] Appropriate modifications will be made, if necessary, or other checklists will be sought, in order to permit effective assessment of studies.

Methods of analysis and synthesis
Study characteristics including patient details, quality scores and clinical outcomes will be tabulated. Key points will be highlighted by a commentary. Data will be pooled, if appropriate, in order to obtain a more precise estimate of clinical effect and to inform the economic appraisal. Aspects of the heterogeneity of available clinical trials will be explored statistically and considered in detail if relevant.

Methods of estimating quality of life, costs, and cost-effectiveness
Our economic evaluation will aim to examine the costs and consequences of using aTNF agents versus that of alternative treatments. If possible a clinically sensible decision pathway will be developed and a cost effectiveness or cost utility analysis will be constructed. ~~The~~ An appropriate time horizon for the analysis ~~will~~ might be from diagnosis to around age 16, if sufficient information to populate such a model can be found. Costs and consequences will be examined from an NHS perspective.

F. Handling company submissions

All submissions will be examined in detail. Additional efficacy and safety data, provided by drug companies, and not available in primary publications, will be incorporated into the review if appropriate. Studies not identified in our searches, that meet inclusion and exclusion criteria, will also be incorporated into our review. Any alternative economic models will be assessed and, if appropriate, will be used to modify our own approach.

G. Research in Progress

This review is concerned with etanercept and infliximab. However, a summary of other anti-TNF therapies is to be included in the Technology Assessment Report on anti-TNF therapies in adults with rheumatoid arthritis. Paediatric clinical research in progress will be identified.

If recommendations for further research are made, account will be taken of the special ethical considerations relevant to research in children and International Conference on Harmonisation guidelines on paediatric clinical trials.

H. Project Management

a. Timetable / Milestones
Submission of protocol: 2 March 2001 (delayed as a result of late commissioning)
Submission of progress report: 4 May 2001
Submission of draft report: 8 June 2001

b. Competing interests
Dr Carole Cummins is an investigator on a research proposal approved by the British Paediatric Rheumatology Group for a biologics and new drug paediatric rheumatology register. Funding is to be sought from Wyeth Pharmaceutical Company.

Dr Paresh Jobanputra is a Consultant Rheumatologist and a member of the British Society for Rheumatology. He is engaged in a multi-centre clinical trial of etanercept plus placebo versus ethanercept plus sulphasalzine. This trial in sponsored by Wyeth Ayerst, manufacturers of ethanercept. He has no personal financial interest in this trial or in Wyeth Ayerst. He is a member of the British Society for Rheumatology.

None of the other authors have any competing interests.

c. External reviewers:

The rapid review will be subject to external peer review by at least two experts. These reviewers will be chosen according to academic seniority and content expertise and will be agreed with NCCHTA. We recognise that methodological review will be undertaken by the NICE secretariat and Appraisal Committee, but if the rapid review encounters particularly challenging methodological issues we will organise independent methodological reviews. External expert reviewers will see a complete and near final draft of the rapid review and will understand that their role is part of external quality assurance. Where the review contains data that is regarded as 'commercial in confidence' we will require peer reviewers to sign a copy of the NICE Confidentiality Acknowledgement and Undertaking. We will return peer reviewers' signed copies to NCCHTA. Comments from external reviewers and our responses to these will be made available to NCCHTA in strict confidence for editorial review and approval.

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