Randomized Controlled Trial Evaluating a Standardized Strategy for Uveitis Etiologic Diagnosis (ULISSE)

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• PURPOSE: To prospectively assess the efficiency of a standardized diagnostic approach, compared to an open strategy, for the etiologic diagnosis of uveitis.

• DESIGN: Noninferiority, prospective, multicenter, clustered randomized controlled trial.

• METHODS: Consecutive patients with uveitis, who visited 1 of the participating departments of ophthalmology, were included. In the standardized group, all patients had a minimal evaluation regardless of the type of uveitis (complete blood count, erythrocyte sedimentation rate, C-reactive protein, tuberculin skin test, syphilis serology, and chest radiograph) followed by more complex investigations according to ophthalmologic findings. In the open group, the ophthalmologist could order any type of investigation. Main outcome was the percentage of etiologic diagnoses at 6 months.

• RESULTS: Nine hundred and three patients with uveitis were included from January 2010 to May 2013 and the per-protocol population comprised 676 patients (open 373; standardized 303). Mean age at diagnosis was 46 years. Anatomic distribution of uveitis was as follows: anterior (60.8% and 72.3%, $P = .0017$), intermediate (11.7% and 12.3%, $P = .8028$), posterior (17.8% and 8.2%, $P = .0004$), and panuveitis (15.3% and 15.2%, $P = .9596$). An etiologic diagnosis was established in 54.4% of cases in the open group and 49.5% in the standardized group ($P = .2029$). The difference between both strategies (standardized minus open) was −4.9% (95% CI [−12.5%; 2.6%]). There were more investigations in the open group than in the standardized group (5371 vs 3759, $P < .0001$).

• CONCLUSION: The standardized strategy appears to be an efficient diagnostic approach for the etiologic diagnosis of uveitis, although its noninferiority cannot be proved. (Am J Ophthalmol 2017;■:■–■. © 2017 Elsevier Inc. All rights reserved.)

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UVEITIS IS THE THIRD-LEADING CAUSE OF BLINDness worldwide and currently accounts for approximately 10% of preventable vision loss in the United States and up to 15% worldwide.[1–3] The etiologic diagnosis of uveitis is important for prognosis and therapeutics but the etiology remains uncertain or unknown in 30%–70% of cases.[4–12]

So far, the strategy for selecting investigations has been evaluated in only a few retrospective studies and relies on the opinion of experts. Some authors have proposed a minimal routine evaluation common to all kinds of uveitis. For instance, Smith and Rosenbaum[13] and Rosenbaum[14] routinely recommend a chest radiograph and serologic tests for syphilis. Kijlstra[15] orders a complete blood count (CBC), an erythrocyte sedimentation rate (ESR), a syphilis serology, a human leukocyte antigen (HLA) determination, and a serum angiotensin-converting enzyme (ACE), and McCluskey and associates[16] perform in all chronic uveitis a chest radiograph, a syphilis serology, and an ACE.

On the other hand, Harper[17] recommend a tailored approach according to the anatomic type of uveitis. Similarly, Jabs and Busingye[18] argued, in a recent review, that

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investigations should be selected based on the pretest probabilities estimated according to the ophthalmologic features and on the therapeutic implications. Thus, they contended that serologic screening for syphilis, chest radiography, and liver enzymes are the only tests appropriate in all forms of uveitis. They suggest that the ophthalmologic findings guide the use of other investigations: for instance, HLA-B27 in acute anterior uveitis or testing for tuberculosis in Eales disease, potential choroidal granuloma, and serpiginous-like choroiditis.

In a previous retrospective study, we evaluated the utility of various diagnostic tests.[19] Most patients had an extensive evaluation regardless of the type of uveitis. This study showed that serologic tests for infectious agents, immunologic tests, and orthopantomograms, radiographs of the sinuses and of the sacroiliac joints, were consistently unhelpful for identifying the cause of uveitis, when ordered in the absence of clinical orientation.

We then developed a standardized diagnostic strategy for uveitis incorporating data from recent studies and expert opinions pointing out the underestimation of sarcoidosis by chest radiography and the usefulness of chest computed tomography (CT) scan,[20] nuclear imaging techniques,[21] and bronchoalveolar lavage (BAL)[22–24] for the diagnosis of sarcoidosis. In addition, our strategy involves anterior chamber tap in patients with acute anterior uveitis when a herpesvirus infection is suspected, and/or a vitrectomy in patients with suspected lymphoma[25,26] or severe uveitis resistant to current treatment.[27,28]

Our strategy is a tailored approach according to the anatomic type of uveitis and clinical findings. The first step is common for all types of uveitis and includes a minimal evaluation with nonexpensive laboratory investigations similar to those recommended by several authors.[13–16] The second and third steps include more complex investigations according to ophthalmologic findings, similar to Harper's strategy.[17]

The main aim of the ULISSE study (Uveitis: cLIical and medicoeconomic evaluation of a Standardized Strategy of the Etiological diagnosis) was to assess the efficiency of this standardized diagnostic approach, compared with an open strategy where physicians could perform any diagnostic test.

METHODS

• **ETHICS:** This study has been approved in a prospective manner by the institutional review board (Comité de Protection des Personnes sud est IV) and conducted in accordance with the Declaration of Helsinki of 2008. All patients provided written informed consent for participation in the research, and the database used for the purpose of this study was reported to the Commission Nationale de l'Informatique et des Libertés. This study was registered at ClinicalTrials.gov under the Unique Identifier NCT01162070 on July 12, 2010.

• **STUDY DESIGN:** This was a noninferiority, open label, prospective, multicenter, clustered randomized controlled trial.

In this study, the efficiency of 2 different strategies was evaluated for the etiologic diagnosis of uveitis. The first strategy was an "open strategy" in which the ophthalmologist, after determining the anatomic type of uveitis, was free to order any investigation he or she thought necessary and to refer the patient to an internist.

The second strategy was a "standardized" one. The first step was common for all types of uveitis. An ophthalmologist and an internist examined the patient, determined the anatomic type of uveitis, and prescribed a minimal evaluation regardless of the type of uveitis (CBC, ESR, C-reactive protein, tuberculin skin test, syphilis serology, and chest radiograph). They could also order extra diagnostic tests guided by clinical or paraclinical findings. If no diagnosis was made at the end of this first step, the internist ordered more complex investigations according to the anatomic type of uveitis (as shown in Table 1), and could order extra diagnostic tests guided by paraclinical findings. If no diagnosis was established with the standardized strategy, physicians were authorized to perform free investigations, but this was considered a failure of the standardized strategy (Figure 1). In addition, if physicians did not perform some of the algorithm's investigations (except for the third step's invasive investigations), or performed free investigations before the end of the third step, it was considered a major protocol deviation.

• **PATIENTS:** This study included consecutive patients with uveitis who visited 1 of the participating departments of ophthalmology from June 23, 2010 to May 31, 2013 and gave written informed consent. The diagnosis of uveitis was established by ophthalmologists in tertiary referral centers, according to the Standardization of Uveitis Nomenclature.[29] Exclusion criteria were patients of less than 18 years of age (which is why the evaluation of chronic anterior uveitis did not include antinuclear antibodies, since juvenile idiopathic arthritis usually begins in childhood), under law protection or guardianship, or pregnant women. Patients who had a surgery or a trauma, a known pathology likely to be the cause of the uveitis, a specific ocular disease diagnosed by ophthalmic examination only, toxoplasmosis infection, human immunodeficiency virus, or a severe retinal vasculitis requiring an urgent treatment (defined by visual acuity of less than 20/200) were also excluded.

At inclusion, each patient received an ophthalmic examination consisting of visual acuity recordings (Snellen scale), slit-lamp examination, intraocular pressure measurement, and dilated fundus examination with indirect ophthalmoscopy. Ancillary testing such as fluorescein angiography and optical coherence tomography were

TABLE 1. Investigations in the Standardized Strategy for the Etiologic Diagnosis of Uveitis

1st Stage	2nd Stage: Investigations Guided by the Anatomic Type of Uveitis OR Guided by Clinical and Paraclinical Findings or Medical History		
	Type	2nd step	3rd step
1st step: systematic investigations CBC ESR, CRP Tuberculin skin test Syphilis serology Chest radiograph	Acute anterior uveitis	• HLA-B27 if no argument for a herpesvirus infection	• Anterior chamber tap if HLA-B27 negative
	Chronic anterior uveitis	• ACE • Chest CT	• None
	Chronic granulomatous uveitis or multifocal choroiditis	• ACE • Chest CT	• Salivary gland biopsy • Bronchoscopy and BAL • 18F-FDG PET or 67Ga scintigraphy
Then investigations guided by clinical, ophthalmologic, and medical history findings	Chronic intermediate uveitis	• ACE • Chest CT	• Lumbar puncture • Brain MRI
	Chronic posterior or panuveitis	• Toxoplasma serology • ACE • Chest CT	• Lumbar puncture • Brain MRI
	Isolated retinal vasculitis	• Complement • Antinuclear antibodies • Antiphospholipid antibodies • Antineutrophil cytoplasmic antibodies	• None
	Severe and/or corticoresistant uveitis	• Anterior chamber tap: cytology, interleukins, herpes PCR, mycobacterium tuberculosis PCR, universal PCR…	• Vitrectomy (if lymphoma suspected)

ACE = angiotensin-converting enzyme; BAL = bronchoalveolar lavage; CBC = complete blood count, CRP; C-reactive protein; CT = computed tomography; ESR = erythrocyte sedimentation rate, 18F-FDG PET = 18F-fluorodeoxyglucose positron emission tomography; HLA = human leukocyte antigen; MRI = magnetic resonance imaging; PCR = polymerase chain reaction.

Note: If a patient has uveitis with several anatomic characteristics, all corresponding investigations must be done.

performed when necessary. Ophthalmologists involved in the study were residents, fellows, attending physicians, or chief physicians.

Patients were followed for a period of 6 months. Ophthalmologists and internists established the etiologic diagnosis at 6 months whenever possible. If there was no diagnosis, an internist reexamined patients at 12 months (except for acute anterior uveitis) to search for new symptoms.

• **OUTCOMES:** The primary outcome was the percentage of patients having an etiologic diagnosis 6 months after the inclusion in the study for both strategies. Only diagnoses made at the end of the standardized strategy were recorded in this arm of the study; all diagnoses made after by the free authorized examinations in this same arm led to standardized strategy failure.

In the standardized strategy, secondary outcomes were the percentage of patients having an established etiologic diagnosis at the end of each step and the ratio of free complementary investigations that contributed to an etiologic diagnosis.

• **DEFINITIONS:** The Standardization of Uveitis Nomenclature[29] was used throughout this study for the anatomic classification of uveitis. Infectious uveitis was diagnosed by a positive culture or polymerase chain reaction in ocular fluid, blood, cerebrospinal fluid, or tissue biopsy. The diagnosis could also be established by a positive serology or a therapeutic test for fastidious bacteria.[30] For the diagnosis of intraocular tuberculosis we used the criteria recommended by Gupta and associates.[31]

With regard to rheumatologic and ophthalmic disorders, we used the ASAS criteria for spondyloarthritis,[32,33] the International Study Group criteria for Behçet disease,[34] the revised diagnostic criteria for Vogt-Koyanagi-Harada disease,[35] the international conference consensus criteria for the diagnosis of birdshot chorioretinopathy,[36] and the 2010 revised McDonald criteria for multiple sclerosis.[37] For sarcoidosis, in the absence of histologic proof, we used both the international criteria for the diagnosis of ocular sarcoidosis[38] and Abad's criteria.[39] Finally, we used Mandeville and associates' criteria for the diagnosis of tubulointerstitial nephritis and uveitis syndrome (TINU).[40]

• **SAMPLE SIZE DETERMINATION:** Assuming that an etiology would be found in 60% of patients at 6 months and using a noninferiority margin of 10%, a total sample size

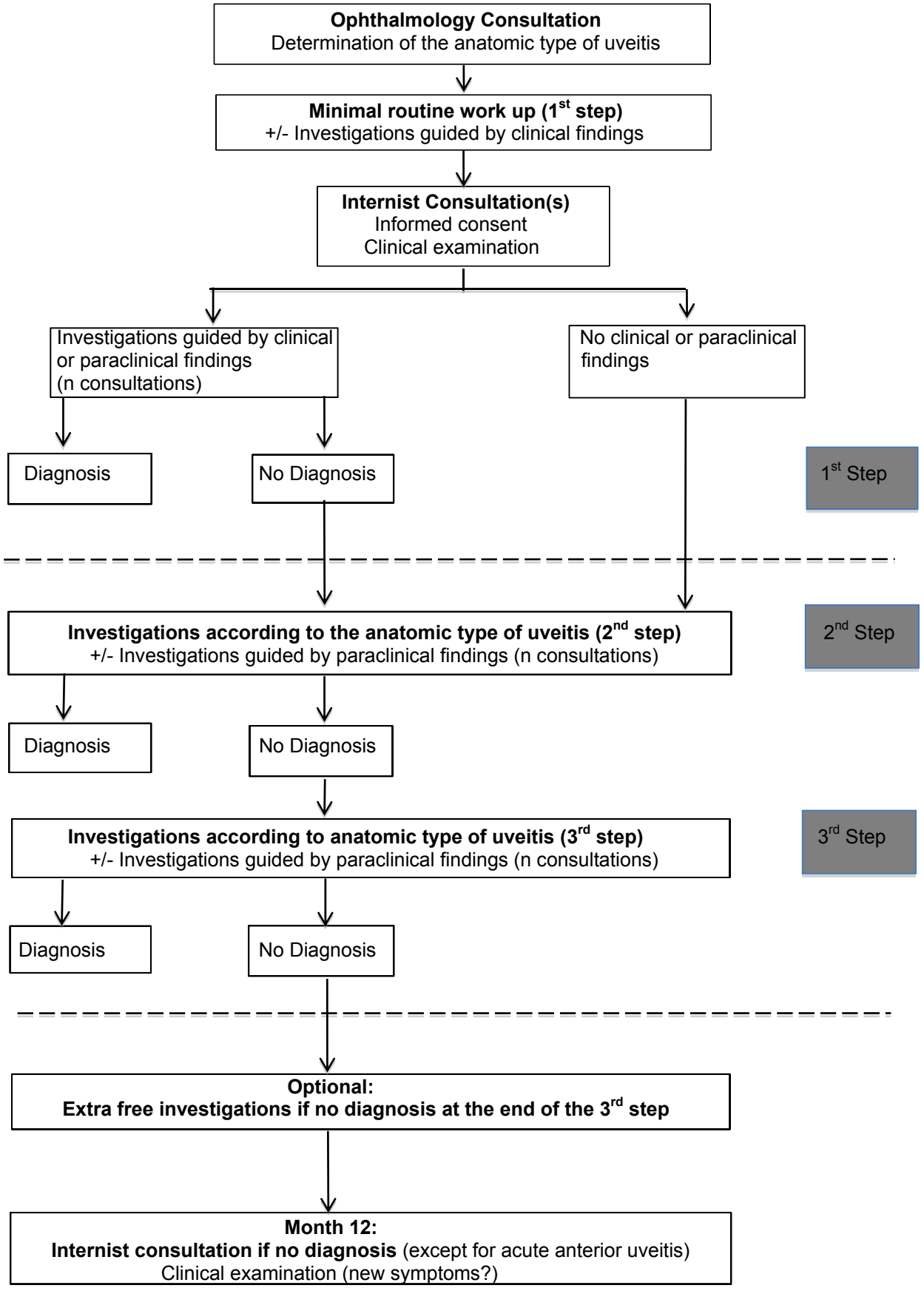

FIGURE 1. Uveitis etiologic diagnosis study design in the standardized group.

of 754 subjects yielded more than 80% power for establishing noninferiority using a 2.5% alpha. We assumed that an etiology would be found in 60% of cases because in a previous retrospective study conducted by the same investigators, the rate of diagnoses was 60.6%.[19]

The dropout rate was set at 3% and the intraclass correlation coefficient was 0.001 (which corresponds to an inflation factor of 1.15). Therefore, a total sample size of 894 subjects was calculated.

• **RANDOMIZATION:** Hospitals participating in the study were randomized by a computer (Proc PLAN SAS software version 9.3; SAS Institute Inc., Cary, North Carolina, USA) into clusters with stratification according to the presence (or not) of an ophthalmologic emergency department in the hospital, because there are more acute anterior uveitis cases in hospitals with ophthalmologic emergency departments.

• **STUDY POPULATION:** We defined 2 populations for the analysis. The per-protocol population comprised all patients who were followed up and for whom the primary outcome was reported, without major protocol deviations. The full analysis set population comprised all patients who were followed up and for whom the primary outcome was reported. The analysis of the primary outcome was performed on the per-protocol population and also on the full analysis set.[41]

• **STATISTICAL ANALYSIS:** Initial characteristics were compared between groups with a Student *t* test for quantitative variables (or Mann-Whitney test in case of nonnormality) or with a χ^2 test for qualitative variables (or Fisher exact test when χ^2 hypotheses were not fulfilled). Analysis of the primary outcome was performed on the per-protocol population. The difference between the percentage of patients with an etiologic diagnostic in both groups was computed along with a standard 95% confidence interval (CI) and with a 95% CI using Klar and Doner's method for cluster randomized trials, and was compared with the noninferiority margin. The same analysis was performed on the full analysis set (intention-to-treat analysis). Other analyses included an adjustment with propensity scores. A subgroup analysis on anatomic types was also performed.

For the analysis of secondary outcomes, which were performed on the per-protocol population, the parameters were presented as means (standard deviation) and medians (minimum and maximum) and compared using a Student *t* test (or Mann-Whitney test in case of nonnormality) for quantitative variables or in terms of numbers (percentage) and compared using a χ^2 test (or Fisher exact test when conditions for χ^2 were not fulfilled) for qualitative variables.

All analyses were performed using SAS software version 9.3 (SAS Institute Inc, Cary, North Carolina, USA).

RESULTS

• **BASELINE DEMOGRAPHIC CHARACTERISTICS:** Between June 2010 and May 2013, 903 patients with uveitis who visited 1 of the 23 participating departments of ophthalmology were included and randomized (Figure 2, and Supplemental Table 1; Supplemental Material available at AJO.com). As some patients were lost to follow-up (standardized 111; open 19), the full analysis set population comprised 709 patients (Supplemental Table 2; Supplemental Material available at AJO.com). In the standardized group, patients lost to follow-up were mostly men (52.3%) who were active (67.3% had a professional activity). The most frequent type of uveitis was anterior (88.2%), the onset sudden (90%), and the duration limited (89.9%). The per-protocol population comprised 676 patients (standardized 303; open 373).

Mean age at inclusion was 47.3 (± 16.2) years in the standardized group and 45.8 (± 15.9) years in the open group ($P = .2295$). There were 184 women in the standardized group and 181 women in the open group (60.7% vs 48.5%, $P = .0015$).

• **OPHTHALMOLOGIC CHARACTERISTICS:** Ophthalmologic characteristics are presented in Table 2. The 2 arms were not comparable with regard to ophthalmologic findings: there were statistically more anterior (72.3% and 60.8%, $P = .0017$) and acute uveitis (69.6% and 60.7%, $P = .0118$) in the standardized group, whereas recurrent (16.9% and 9.6%, $P = .0118$) and posterior uveitis (17.8% and 8.2%, $P = .0004$) were more frequent in the open group.

• **PRIMARY OUTCOME:** At 6 months, an etiologic diagnosis was determined in 152 out of 303 patients (50.4%) in the standardized group and in 203 out of 373 (54.4%) in the open group ($P = .2702$). Among the 152 diagnoses in the standardized group, 2 patients had an etiologic diagnosis thanks to free complementary investigations and were considered as a failure of the strategy (a urinanalysis revealed a TINU syndrome, and a serum ACE and lysozyme revealed a possible sarcoidosis).

Thus, in per-protocol analysis, the standardized strategy was successful in 49.5% (150/303) of cases and the open strategy in 54.4% (203/373) of cases ($P = .2029$). Intention-to-treat analysis revealed a success rate of 47.5% (159/335) in the standardized group and 54.3% (203/374) in the open group ($P = .0115$). The difference between both strategies (standardized minus open) was −4.9% (95% CI: −12.5%; 2.6%) in the per-protocol analysis and −6.8% (95% CI: −14.4%; 0.7%) in the intention-to-treat analysis. These comparisons were inconclusive: the standardized strategy was neither inferior nor noninferior to the open strategy because the 95% CI

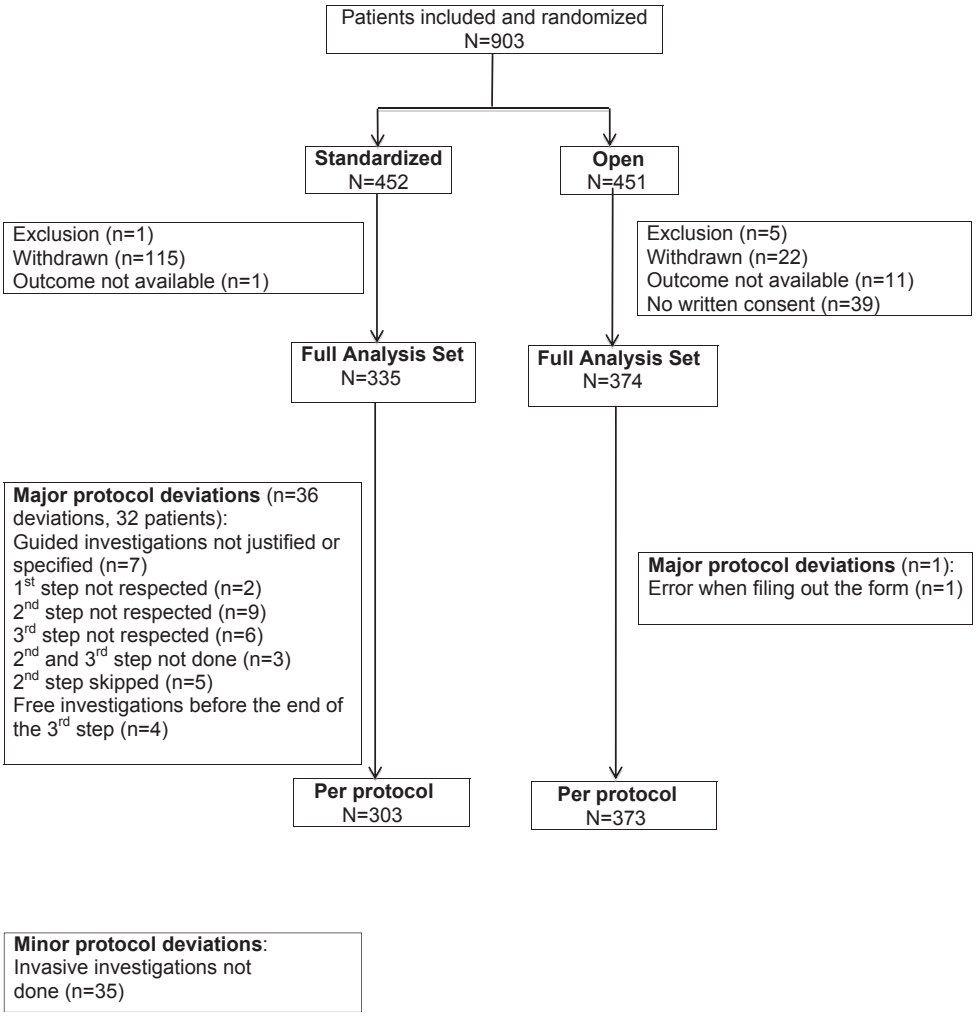

FIGURE 2. Uveitis etiologic diagnosis trial study flow chart.

included zero and the noninferiority margin. Adjustment on clusters yielded broader confidence intervals, and the comparison was still inconclusive. Analysis with propensity scores gave similar results.

We also performed subgroup analysis to determine the diagnostic yield within each anatomic type in both groups. The success rate was higher in the standardized strategy for panuveitis with a 95% CI excluding the noninferiority margin, but this was no longer the case after adjustment on clusters (Table 3).

Finally, in per-protocol analysis, there were more investigations in the open group than in the standardized group (5371 vs 3759, $P < .0001$), with an average of 15.39 investigations per patient in the open group vs 12.41 in the standardized group ($P < .0001$).

• **DIAGNOSES:** Among classified uveitis in the 2 groups, the most frequent forms were systemic diseases (60.8%), followed by infections (25.1%), ocular-specific disorders (10.7%), masquerade syndromes (1.7%), and medications (1.4%). The most common entities included HLA-B27-associated uveitis (22%), sarcoidosis (18%), spondyloarthritis (11%), tuberculosis (10.7%), and herpesvirus infections (8.5%). These 5 entities accounted for 70% of all diagnoses. On the other hand, Behçet disease and syphilis accounted for only 4.2% and 1.7% of cases, respectively (Table 4).

• **STANDARDIZED STRATEGY:** In the standardized strategy, 16 patients had a clinical diagnosis, although with regard to ophthalmic entities, the diagnosis was not initially ascertained at time of inclusion (5 Fuchs heterochromic iridocyclitis, 6 herpesvirus infection, 2 Vogt-Koyanagi-Harada disease, 1 spondyloarthritis, 1 birdshot chorioretinopathy, and 1 pars planitis). For the remaining patients, the diagnosis was established at the first step in 75.7% of cases (103/136), at the second step in 21.3% of cases (29/136), and at the third step in 1.5% of cases (2/136). At the end of the third step, 189 "free" extra investigations were performed in 43 patients,

TABLE 2. Baseline Clinical Characteristics in Both Groups in Investigation of Standardized Strategy for the Etiologic Diagnosis of Uveitis

Characteristic	Standardized	Open	*P* Value[a]
Mean age at inclusion, y (SD)	47.3 (16.18)	45.83 (15.93)	.2295
Sex			
Female	184 (60.7)	181 (48.5)	.0015
Male	119 (39.3)	192 (51.5)	
Professional activity			
Not reported	8	15	.0016
Yes	198 (67.1)	245 (68.4)	
No	97 (32)	113 (30.3)	
Onset			
Not reported	1	5	.0576
Sudden	233 (77.2)	260 (70.7)	
Insidious	69 (22.8)	108 (29.3)	
Course			
Not reported	0	7	.0118
Recurrent	29 (9.6)	62 (16.9)	
Acute	211 (69.6)	222 (60.7)	
Chronic	63 (20.8)	82 (22.4)	
Duration			
Not reported	0	7	.1115
Limited	231 (76.2)	259 (70.8)	
Persistent	72 (23.8)	107 (29.2)	
Panuveitis[b]			
Not reported	0	1	.9596
Yes	46 (15.2)	57 (15.3)	
No	257 (84.8)	315 (84.7)	
Anterior uveitis[b]			
Not reported	3	3	.0017
Yes	217 (72.3)	225 (60.8)	
No	83 (27.7)	145 (39.2)	
Intermediate uveitis[b]			
Not reported	10	4	.8028
Yes	36 (12.3)	43 (11.7)	
No	257 (87.7)	326 (88.3)	
Posterior uveitis[b]			
Not reported	11	2	.0004
Yes	24 (8.2)	66 (17.8)	
No	268 (91.8)	305 (82.2)	
Granulomatous uveitis[b]			
Not reported	0	7	.1740
Yes	71 (23.4)	70 (19.1)	
No	232 (76.6)	296 (80.9)	
Peripheral multifocal choroiditis[b]			
Not reported	0	9	.1044
Yes	19 (6.3)	13 (3.6)	
No	284 (93.7)	351 (96.4)	
Isolated retinal vasculitis			
Not reported	0	10	.4433
Yes	18 (5.9)	27 (7.4)	
No	285 (94.1)	336 (92.6)	
Severe uveitis (visual acuity <20/200)			
Not reported	0	11	.2445
Yes	5 (1.7)	11 (3)	
No	298 (98.3)	351 (97)	
Corticoresistance and/or dependence >20 mg			
Not reported	1	11	.2281*
Yes	1 (0.3)	5 (1.4)	
No	301 (99.7)	357 (98.6)	
Laterality			
Not reported	0	1	.1455
Bilateral	108 (35.6)	153 (41.1)	
Unilateral	195 (64.4)	219 (58.9)	

Values are n (%) unless otherwise specified.

[a]*P* values are for χ^2 test or Student *t* test unless * is specified (Fisher exact test or Mann-Whitney test).

[b]Anatomic types are not mutually exclusive.

but this enabled a diagnosis in only 2 patients (see above).

• **FOLLOW-UP:** Finally, only 20 patients in the standardized group and 12 in the open group had a consultation with an internist at 12 months. Only 1 diagnosis (psoriatic arthritis) was established in the standardized group during follow-up.

DISCUSSION

WE REPORT A PROSPECTIVE STUDY THAT ASSESSES A STANdardized strategy for the etiologic diagnosis of uveitis, compared with an open strategy. An etiologic diagnosis was established in approximately half of the patients in both groups, which is similar to the results of previous studies.[7,9,10,28] Nevertheless, the comparison of both strategies was inconclusive: the standardized strategy was neither inferior nor noninferior to the open strategy.

Furthermore, in the standardized group, investigations guided by clinical or paraclinical findings were often helpful in establishing the cause of uveitis, which was not the case for investigations ordered in the absence of clinical orientation (extra free investigations). In addition, significantly fewer investigations were performed in this group.

The main limit to our study is that clinical characteristics of patients at inclusion differed between groups, with regard to ophthalmologic findings and sex. In addition, although information about the demographics, such as race/ethnicity, would have been useful for the applicability

TABLE 3. Standardized Strategy for the Etiologic Diagnosis of Uveitis: Success Rate Within Each Anatomic Subgroup

	Standardized	Open	Difference	95% CI	95% CI Adjusted for Cluster
Anterior uveitis	98/217 (45.2)	122/225 (54.2)	−9.1	−18.4; 0.2	−27.6; 9.5
Intermediate uveitis	17/36 (47.2)	19/43 (44.2)	3.0	−19.0; 25.1	−19.3; 25.3
Posterior uveitis	12/24 (50.0)	39/66 (59.1)	−9.1	−32.4; 14.2	−42.0; 23.8
Panuveitis	33/46 (71.7)	35/57 (61.4)	10.3	−7.8; 28.5	−17.2; 37.9

Values are n (%).

TABLE 4. Etiologic Diagnosis of Uveitis at 6 Months in Both Study Groups

	Total	Standardized	Open	*P* Value[a]
Form				
Specific ocular disease	38 (10.7)	15 (9.9)	23 (11.3)	.0795*
Infectious disease	89 (25)	35 (23)	54 (26.6)	
Systemic disease	216 (60.8)	98 (64.5)	118 (58.1)	
Masquerade syndrome	6 (1.7)	0 (0)	6 (3)	
Medication	5 (1.4)	4 (2.6)	1 (0.5)	
Other	1 (0.3)	0 (0)	1 (0.5)	
Specific diagnosis				
HLA-B27-associated uveitis	78 (22)	34 (22.4)	44 (21.7)	.0403
Sarcoidosis	64 (18)	23 (15.1)	41 (20.2)	
Spondyloarthritis	39 (11)	24 (15.8)	15 (7.4)	
Tuberculosis	38 (10.7)	16 (10.5)	22 (10.8)	
Herpesvirus	30 (8.5)	10 (6.6)	20 (9,8)	
Behçet disease	15 (4.2)	4 (2.6)	11 (5.4)	
Birdshot chorioretinopathy	12 (3.4)	4 (2.6)	8 (3.9)	
Fuchs heterochromic iridocyclitis	11 (3.1)	5 (3.3)	6 (3)	
Toxoplasmosis	6 (1.7)	0 (0)	6 (3)	
Syphilis	6 (1.7)	3 (2)	3 (1.5)	
Vogt-Koyanagi-Harada disease	5 (1.4)	5 (3.3)	0 (0)	
Lymphoma	4 (1.1)	0 (0)	4 (2)	
Medication	4 (1.1)	3 (2)	1 (0.5)	
Posner-Schlossman syndrome	3 (0.8)	0 (0)	3 (1.5)	
Pars planitis	3 (0.8)	3 (2)	0 (0)	
Acute posterior multifocal placoid pigment epitheliopathy	3 (0.8)	1 (0.7)	2 (1)	
Multiple sclerosis	2 (0.6)	1 (0.7)	1 (0.5)	
Tubulointerstitial nephritis and uveitis syndrome	2 (0.6)	1 (0.7)	1 (0.5)	
Cat scratch disease	1 (0.3)	1 (0.7)	0 (0)	
Toxocarosis	1 (0.3)	1 (0.7)	0 (0)	
Multifocal choroiditis	1 (0.3)	1 (0.7)	0 (0)	
Phacoantigenic uveitis	1 (0.3)	0 (0)	1 (0.5)	
Others	26 (7.3)	12 (7.9)	14 (6.9)	

Values are n (%).
[a]*P* values are for χ^2 test unless * is specified (Fisher exact test).

to other populations, this information has not been collected because, in France, it is not allowed to collect data referring to race or ethnic origin, except in specific cases.

There was imbalance between groups with regard to baseline characteristics because patients were not randomized individually but were randomized by clusters, and although there were 23 clusters, a small number of clusters

included the majority of patients. Therefore, randomization was less efficient.

With regard to ophthalmologic findings, the anatomic distribution of uveitis differed between groups: anterior uveitis was significantly more frequent in the standardized group and posterior uveitis was significantly more frequent in the open group. Because the diagnostic yield of uveitis differs according to the anatomic type of uveitis,[4,7–12] we performed subgroup analysis. They showed that the diagnostic yield within each anatomic type did not differ significantly between the 2 strategies.

Another limit of our study is that, in the standardized group, 115 out of 452 patients (25.4%) were lost to follow-up and there were major protocol deviations in 32 out of 335 patients (9.5%). This limits the power of our study as well as its validity, and calls into question whether the standardized diagnostic approach can be successfully implemented in routine clinical practice.

Most of the patients lost to follow-up were young, active men with acute anterior uveitis. Because approximately 50% of patients with acute anterior uveitis are HLA-B27-positive,[42] if they had been able to go through the first 2 steps in the standardized strategy this would have probably increased the diagnostic yield in this group.

Furthermore, in the standardized strategy 35 patients did not undergo some invasive investigations, such as lumbar puncture in intermediate and chronic uveitis, bronchoscopy in chronic granulomatous uveitis or multifocal choroiditis, and anterior chamber tap in acute anterior uveitis. Physicians were probably reluctant to order these investigations, especially in patients who were in remission, because of their invasiveness.

In conclusion, ULISSE is a multicenter, prospective, randomized study evaluating the effectiveness of a standardized strategy compared with an open strategy. In the standardized strategy, among patients with a diagnosis, 98.7% were established thanks to the strategy only and investigations ordered in the absence of clinical orientation were almost always unhelpful for identifying the cause of uveitis. In both groups, approximately half of the patients had an etiologic diagnosis at 6 months. The standardized strategy was neither inferior nor noninferior to the open strategy. However, significantly more investigations were performed in the open group. Further studies are needed to evaluate the cost-efficiency of each strategy, and the evaluation of the diagnostic yield of each test is necessary to clarify the most relevant approach in the diagnosis of uveitis.

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