

# EFFECTIVENESS OF *BIFIDOBACTERIUM LONGUM* 35624 IN THE TREATMENT OF PATIENTS WITH IRRITABLE BOWEL SYNDROME: A SYSTEMATIC REVIEW

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**Abstract – Objective:** The main purpose of this review is to systematize the data on the effectiveness of *Bifidobacterium longum* 35624 in the treatment of patients with irritable bowel syndrome (IBS).

**Materials and Methods:** Studies were searched in the electronic databases MEDLINE/PubMed, EMBASE, Cochrane, and the Russian Science Citation Index (RSCI) based on the Scientific Electronic Library. The analysis included papers published between January 2000 and November 2023 (inclusive).

**Results:** The final analysis included 5 studies in 796 patients with IBS carried out in France (n = 2), Ireland (n = 1), Great Britain (n = 1) and Russia (n = 1). Two studies used the Rome II Diagnostic Criteria for IBS, and three studies used the Rome IV. The conducted studies, the findings of which were summarized in this systematic review, have convincingly shown that the use of *Bifidobacterium longum* 35624 in patients with IBS contributes to the regression of disease symptoms and an improvement in the quality of life. Recent observational studies with different follow-up periods have shown that an extended course of *Bifidobacterium longum* 35624 results in a more pronounced clinical response compared to the standard duration of the probiotic course (30 days).

**Conclusions:** This systematic review has demonstrated that the use of *Bifidobacterium longum* 35624 in patients with IBS, particularly an extended course of up to 3 months, contributes to the regression of disease symptoms and improvement in the quality of life.

**Keywords:** Irritable bowel syndrome, Probiotics, *Bifidobacterium longum* 35624.

## INTRODUCTION

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder manifested by recurring abdominal pain associated with changes in the frequency of bowel movements and/or stool consistency<sup>1-3</sup>. IBS is a common functional gastrointestinal disorder that predominantly



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affects people of working age, representing a significant socio-economic burden<sup>4,5</sup>. A recent meta-analysis, pooling data from 57 studies involving over 400,000 participants, demonstrated that the global prevalence of IBS diagnosed using Rome-IV criteria in the adult population is approximately 3.8% (95% CI: 3.1-4.5)<sup>6</sup>. These epidemiological data align with the results of a recent multinational study using an internet survey of respondents (n = 54,127), which showed a worldwide incidence of IBS of 4.1% (95% CI: 3.9-4.2)<sup>7</sup>.

Despite significant progress in understanding the mechanisms underlying IBS symptoms, there is currently no single etiopathogenetic model for the development of this condition<sup>1,3,8</sup>. However, research over the past 15 years suggests that dysbiotic alterations in the composition and function of the intestinal microbiota play a crucial role in IBS pathogenesis<sup>9,10</sup>. A meta-analysis that summarized the results of 23 studies (n = 1,340) demonstrated that, compared with the control group, patients with IBS experienced a significant decrease in *Lactobacillus* (MD: -0.57 log<sub>10</sub> CFU/g), *Bifidobacterium* (MD: -1.04 log<sub>10</sub> CFU/g); and an increase in *Escherichia coli* (MD: 0.60 log<sub>10</sub> CFU/g), *Enterobacter* (MD: 0.74 log<sub>10</sub> CFU/g)<sup>11</sup>. The relevance of changes in the intestinal microbiota in the development of IBS symptoms is underscored by studies demonstrating the adverse impact of the new coronavirus infection COVID-19 on the disease<sup>12,13</sup>. The latest meta-analysis shows that patients who have recovered from COVID-19 are at a significantly increased risk of IBS compared with controls (OR 6.27, 95% CI: 0.88-44.76)<sup>14</sup>.

Current data on disturbances in the intestinal microbiota in IBS have sparked considerable interest in novel therapeutic approaches, including the use of probiotics in this patient population<sup>9,15</sup>. Meta-analysis demonstrated that probiotic therapy exhibited significantly greater efficacy than placebo in alleviating IBS symptoms (OR 1.82, 95% CI: 1.27-2.60) and improved patients' quality of life (standardized mean difference: 0.29, 95% CI: 0.08-0.50)<sup>15</sup>. Recent meta-analyses<sup>16,17</sup> have also confirmed the beneficial effect of probiotics on IBS symptoms, but this effect depends on the strains included in the probiotic formulations.

One of the most extensively studied probiotic strains in the treatment of IBS is *Bifidobacterium longum* 35624 (formerly *Bifidobacterium infantis* 35624)<sup>9,15</sup>. Experimental studies have shown that *Bifidobacterium longum* 35624 is able to directly bind to the inflamed colonic mucosa and reduce the intestinal barrier dysfunction observed in IBS<sup>18</sup>. In addition, this strain has demonstrated the potential for inducing regression of visceral hypersensitivity, including post-inflammatory<sup>19,20</sup>. The clinical efficacy of *Bifidobacterium longum* 35624 was demonstrated in early controlled studies<sup>21,22</sup>. Despite this, there have been no systematic reviews summarizing the experience with this strain in IBS patients.

The main purpose of this review is to systematize the data on the effectiveness of *Bifidobacterium longum* 35624 in the treatment of patients with IBS.

## MATERIALS AND METHODS

This review was performed according to the principles of preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement. The search for studies was carried out in the electronic databases MEDLINE/PubMed, EMBASE, Cochrane, and the Russian Science Citation Index (RSCI). Titles and abstracts from the above databases were analyzed. The analysis included papers published between January 2000 and November 2023 (inclusive). The following combination of keywords was used to search in MEDLINE/PubMed: bifidobacterium[Title/Abstract] AND 35624[Title/Abstract] AND irritable[Title/Abstract], as well as their closest analogues. The search in the RSCI database was carried out using the following queries, considering morphology: "bifidobacterium" and "35624".

The inclusion criteria for the systematic review were: relevant original studies in peer-reviewed journals in English or Russian; studies with *Bifidobacterium longum* 35624; studies only on the population of patients with IBS. If duplicate results were found in different or the same electronic database, one was selected for the final analysis.

Two researchers (D.N.A. and S.V.C.) independently extracted data using standardized forms. The year of publication, country, study design, and study population of IBS patients were analyzed. Any disagreements were resolved through consensus.

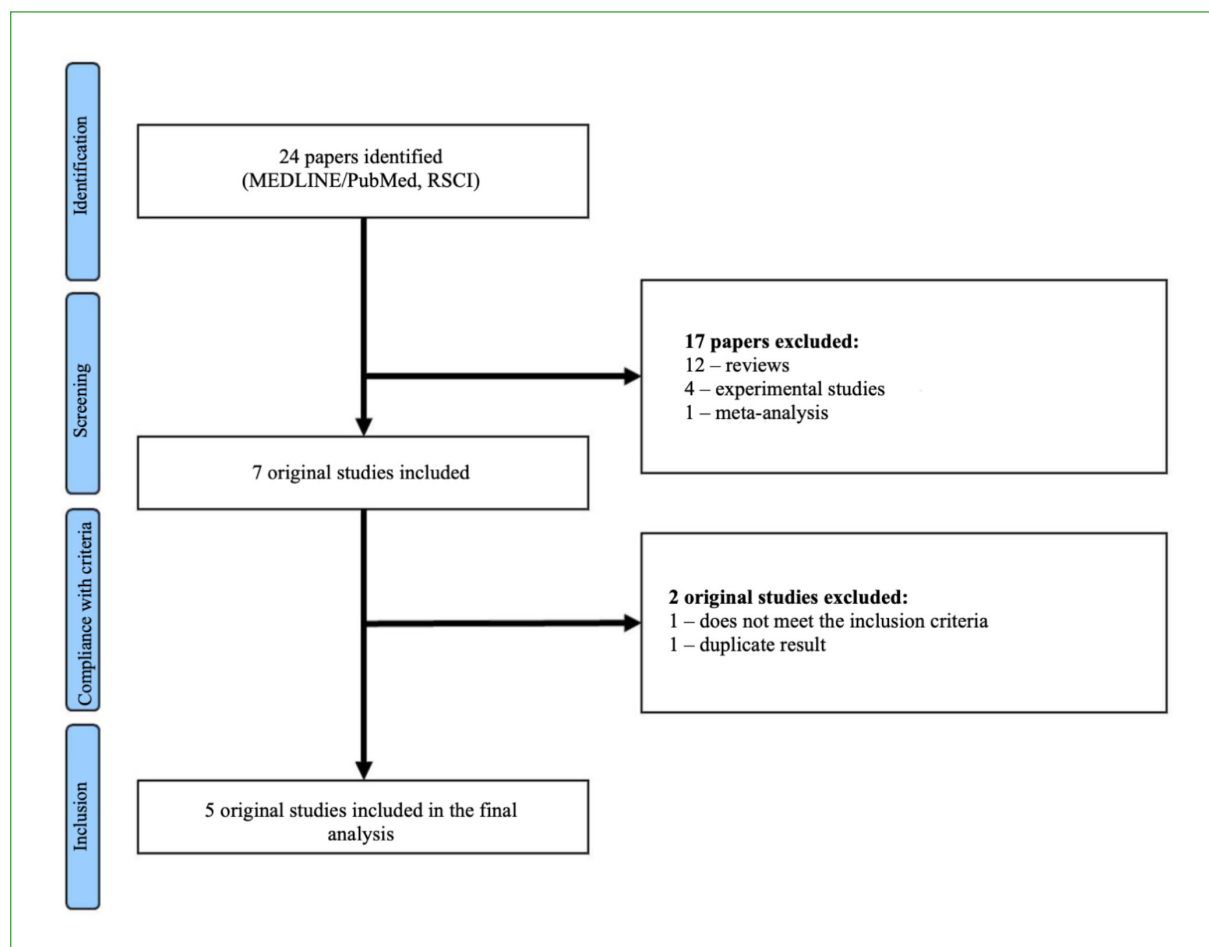
## RESULTS

A search in electronic databases identified 24 published papers for further analysis. Of these, 17 studies were excluded because they were not original works (12 reviews, 4 experimental studies, 1 meta-analysis). The selected 7 studies were analyzed in detail for compliance with the inclusion criteria, after which 2 studies were excluded (1 – did not meet the inclusion criteria; 1 – duplicate result) (Figure 1). Ultimately, the remaining 5 original studies that met the criteria were included in this systematic review<sup>21-25</sup>.

The final analysis included 5 studies in 796 patients with IBS (Table 1) carried out in France (n = 2)<sup>23,25</sup>, Ireland (n = 1)<sup>21</sup>, Great Britain (n = 1)<sup>22</sup> and Russia (n = 1)<sup>24</sup>. Two studies used the Rome II Diagnostic Criteria for IBS<sup>21,22</sup>, and three studies used the Rome IV iteration<sup>23-25</sup>.

O'Mahony et al<sup>21</sup> (2005) conducted the first randomized controlled trial of *Bifidobacterium longum* 35624 ( $1 \times 10^{10}$  CFU) in patients with IBS. The findings of this study indicated that subjects receiving this probiotic strain had a more pronounced improvement in disease symptoms over the course of an 8-week observation period than in the placebo group. At baseline, the IBS patients in the study had an abnormal IL-10/IL-12 cytokine ratio. During therapy with *Bifidobacterium longum* 35624, this ratio was normalized.

A randomized placebo-controlled trial by Whorwell et al<sup>22</sup> (2006) in 362 women with IBS showed a significant reduction in abdominal pain/discomfort on a 6-point Likert scale by week 4 of treatment with *Bifidobacterium longum* 35624 ( $1 \times 10^8$  cfu) compared with the placebo group ( $p = 0.023$ ). The other two probiotic doses ( $1 \times 10^6$  and  $1 \times 10^{10}$  CFU) used in this study were not significantly different from placebo. In addition, this study recorded an improvement in a complex measure of the severity of IBS symptoms (sum of individual



**Figure 1.** Diagram detailing the study selection strategy.

TABLE 1. CHARACTERISTICS OF SELECTED STUDIES.

Study, year	Country	Design	IBS criteria	Population	Probiotic dosage(s)	Study duration	Main outcomes
O'Mahony et al <sup>21</sup> , 2005	Ireland	Randomized placebo-controlled	Rome II	77	1 x 10 <sup>10</sup> CFU	8 weeks	Greater improvement in disease symptoms was observed in the <i>Bifidobacterium longum 35624</i> group during the 8-week follow-up period than in the placebo group. Symptomatic response was associated with normalization of the ratio of anti-inflammatory and pro-inflammatory cytokines (IL-10/IL-12).
Whorwell et al <sup>22</sup> , 2006	UK	Randomized placebo-controlled	Rome II	362	1 x 10 <sup>6</sup> CFU/ 1 x 10 <sup>8</sup> CFU/ 1 x 10 <sup>10</sup> CFU	4 weeks	The <i>Bifidobacterium longum 35624</i> (1 x 10 <sup>8</sup> CFU) was significantly superior to placebo and all other doses of bifidobacteria on the primary efficacy measure of abdominal pain, as well as on the composite score and scores for bloating, bowel dysfunction, incomplete bowel movement, and straining.
Sabaté et al <sup>23</sup> , 2022	France	Observational	Rome IV	278	1 x 10 <sup>9</sup> CFU	30 days	There was a significant reduction in IBS severity compared with baseline. The quality of life of patients was also improved by the treatment.
Solovyova et al <sup>24</sup> , 2022	Russia	Observational	Rome IV	42	1 x 10 <sup>9</sup> CFU	12 weeks	After 12 weeks treatment period there was a significant reduction in IBS severity compared with baseline and improvement the quality of life.
Lenoir et al <sup>25</sup> , 2023	France	Observational	Rome IV	37	1 x 10 <sup>9</sup> CFU	8 weeks	8-week treatment with <i>Bifidobacterium longum 35624</i> was associated with a significant reduction (43.4%) in Total IBS Symptom Score (TISS) compared to baseline. By the end of follow-up, more than 60% of patients achieved a clinically significant reduction in TISS (>30%) and IBS-SSS scores (>50 points).

scores: abdominal pain/discomfort, bloating, and impaired intestinal motility (constipation or diarrhea) on a 15-point scale) by week 4 of therapy, demonstrating a significant improvement compared to the placebo group ( $p = 0.013$ ).

In a large prospective study by Sabaté et al<sup>23</sup> (2022), after 30 d of treatment with *Bifidobacterium longum* 35624, there was a significant reduction in IBS severity compared with baseline (mean  $\pm$  SD overall IBS-SSS score: 208.1  $\pm$  104.8 vs. 303.2  $\pm$  81.5,  $p < 0.001$ ). After the treatment period, there was a significant reduction in IBS severity compared with baseline (mean  $\pm$  SD overall IBS-SSS score: 208.1  $\pm$  104.8 vs. 303.2  $\pm$  81.5,  $p < 0.001$ ). The most notable improvements were observed in patients with more severe IBS: 9.1%, 28.6%, and 49.1% of patients reported an improvement in the group of patients with mild, moderate, and severe disease, respectively. The quality of life of patients was also improved by the treatment (IBS-QoL questionnaire score: 68.8  $\pm$  20.9 vs. 60.2  $\pm$  20.5;  $p < 0.001$ ).

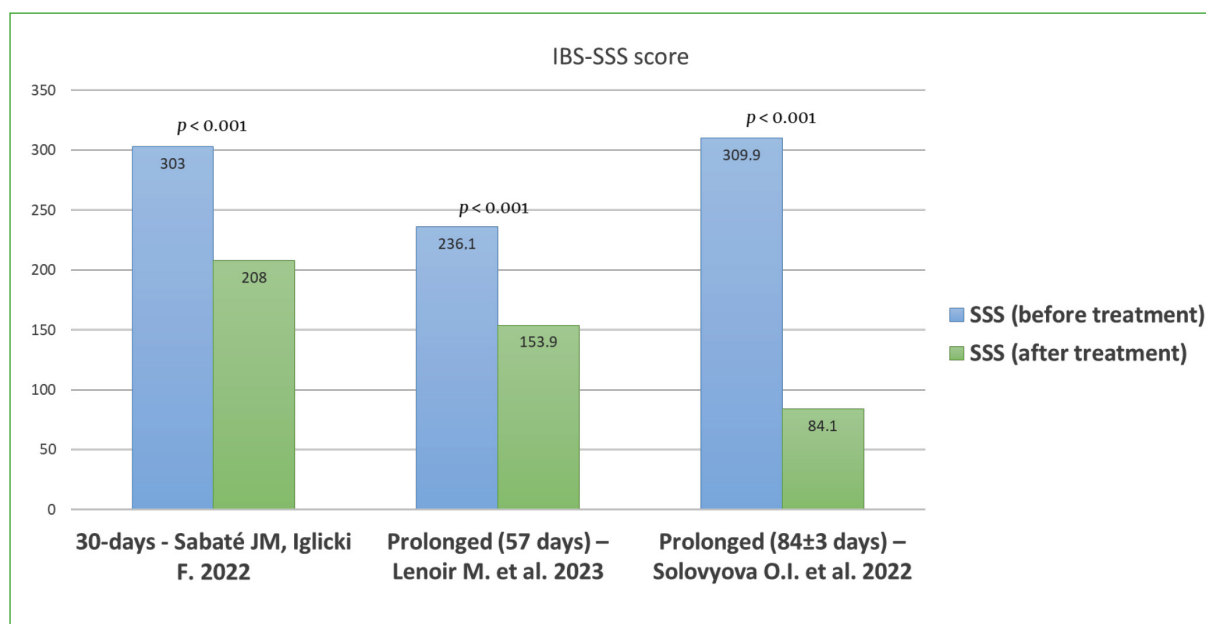
A recently published study by Solovyova et al<sup>24</sup> (2022) in a Russian population of IBS patients demonstrated the ability of *Bifidobacterium longum* 35624 to positively influence IBS symptoms after 14 days of use, while an extended course (for 3 months) exhibited higher efficacy, leading to positive trends in IBS symptoms, visceral sensitivity index, severity and impact on the quality of life. After 12 weeks treatment period there was a significant reduction in IBS severity compared with baseline (mean  $\pm$  SD overall IBS-SSS score: 309.9  $\pm$  62.3 vs. 84.1  $\pm$  67.9,  $p < 0.001$ ) and improvement the quality of life (IBS-QoL questionnaire score: 85.4  $\pm$  12.2 vs. 63.9  $\pm$  14.5;  $p < 0.001$ ).

In an observational study by Lenoir et al<sup>25</sup> (2023), 8-week treatment with *Bifidobacterium longum* 35624 was associated with a significant reduction (43.4%) in Total IBS Symptom Score (TISS) compared to baseline. Additionally, treatment was associated with statistically significant changes over time in the bloating, passage of gas, diarrhea ( $p < 0.0001$  for all three), and abdominal pain ( $p < 0.001$ ). By the end of follow-up, more than 60% of patients achieved a clinically significant reduction in TISS (>30%) and IBS-SSS scores (>50 points). Regression on the IBS-SSS scale over 8 weeks of therapy was 82 points (compared to baseline): 236.1  $\pm$  101.7 at baseline versus 153.9  $\pm$  110.0;  $p < 0.001$ ).

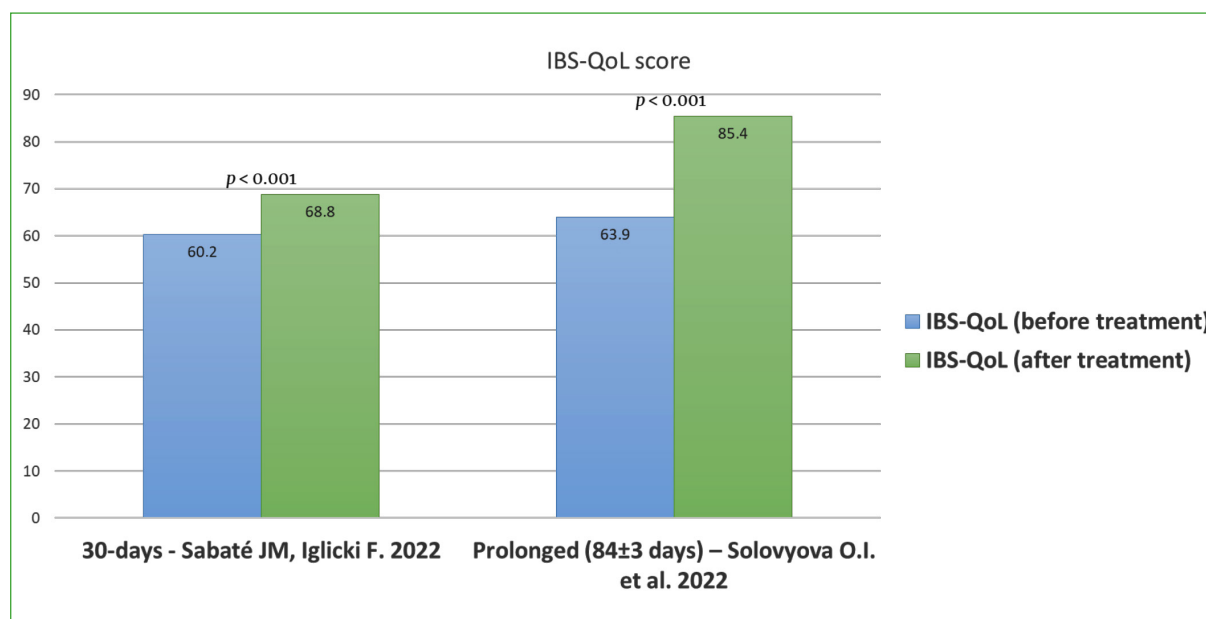
## DISCUSSION

IBS is a common disease that affects people of working age and significantly reduces the quality of life<sup>1-3</sup>. Alterations of the intestinal microbiota are recognized as a key factor in the pathogenesis of IBS, underscoring the importance of incorporating probiotics with established efficacy into the complex therapy for this condition<sup>15</sup>. A recent meta-analysis summarizing the results of 52 randomized controlled trials found that probiotics significantly increased overall response rate (RR: 1.64;  $p < 0.00001$ ), subjective pain relief (RR: 1.50;  $p = 0.0002$ ), and rate of abdominal pain relief (RR: 1.69;  $p < 0.00001$ ) in patients with IBS. Regarding specific genera, *Bifidobacterium* (RR: 1.76;  $p < 0.00001$ ) and *Lactobacillus* (RR: 1.97;  $p = 0.0004$ ) most significantly improved IBS symptoms<sup>26</sup>. However, not every strain of *Bifidobacterium* has the potential to reduce IBS symptoms. A systematic review summarizing the results of 8 randomized controlled trials found that only 50% of the studies found a statistically significant improvement in abdominal pain after taking *Bifidobacterium* supplements compared to placebo<sup>27</sup>.

The conducted studies, the findings of which were summarized in this systematic review, have convincingly shown that the use of *Bifidobacterium longum* 35624 in patients with IBS contributes to regression of disease symptoms and an improvement in the quality of life. Recent observational studies with different follow-up periods have shown that an extended course of *Bifidobacterium longum* 35624 results in a more pronounced clinical response based on the key parameters compared to the standard duration of the probiotic course (30 days). This is vividly illustrated by changes in the scores of the IBS-SSS symptom severity questionnaire (Figure 2), as well as of the IBS-QoL quality of life questionnaire (Figure 3). The studies analyzed in the systematic review included patients with different subtypes of IBS, suggesting that this probiotic strain may be effective for any subtype. This probiotic strain is recommended as a symptomatic treatment for IBS by the WGO, the Scientific Community for Human Microbiome Research (CHMR), and the Russian Gastroenterology Association (RGA)<sup>9,14</sup>.



**Figure 2.** Efficacy of *Bifidobacterium longum* 35624 courses with different duration in IBS patients: IBS-SSS symptom severity questionnaire.



**Figure 3.** Efficacy of *Bifidobacterium longum* 35624 courses with different duration in IBS patients: IBS-QoL quality of life questionnaire.

## CONCLUSIONS

Dysbiosis in patients with IBS constitutes a key element in the pathogenesis and induction of disease symptoms. Prescribing probiotics with proven effectiveness and meeting modern requirements is a justified strategy for optimizing the treatment of such patients. This systematic review has demonstrated that the use of *Bifidobacterium longum* 35624 in patients with IBS, particularly an extended course of up to 3 months, contributes to regression of disease symptoms and improvement in the quality of life.

### **Conflict of Interest**

The authors declare no conflict of interest.

### **Authors' Contributions**

Writing - original draft preparation: D. Andreev, D. Bordin; Supervision and Conceptualization: D. Bordin, I. Maev, S. Cheremushkin. All authors have read and agreed to the published version of the manuscript.

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### **Ethics Approval and Informed Consent**

No additional consent is required for a review of published scientific literature.

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