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Efficacy Of A Collaborative Protocol Between Family Medicine, Laboratory, And Mental Health In Managing Patients With Medically Unexplained Symptoms: Towards A Strategy To Reduce Health Resource Wastage

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Abstract

Background: Medically Unexplained Symptoms (MUS) are a significant source of clinical challenge, which account for 5-11% of patients in primary care and that in turn is the cause of a large part of the wastage of healthcare resources through needless investigations and referrals to specialists. Optimizing patient outcomes while cutting healthcare costs is achievable through an integrated and collaborative approach that treats medical, laboratory, and psychological aspects simultaneously. Objective: To measure the effectiveness of a collaborative multidisciplinary protocol involving Family Medicine, Laboratory Services, and Mental Health in managing MUS patients. The study also aimed to observe changes in resource utilization and clinical outcomes. Methods: This mixed-methods study presents 18-month data on 485 patients with diagnostically confirmed MUS who were managed under the new collaborative protocol. These patients were compared with 520 historical controls who received standard care. The main outcomes were healthcare resource utilization, symptom severity, quality of life, and patient satisfaction. Secondary outcomes examined cost-effectiveness and the clinical course of MUS. Results: The collaborative protocol brought about major reductions in unnecessary investigations (47% reduction, $p<0.001$), specialist referrals (39% reduction, $p<0.001$), and emergency department visits (52% reduction, $p<0.001$). On average, the healthcare costs were reduced by €2,847 per patient per year ($p<0.001$). The patient satisfaction rate went up from 52% to 89% ($p<0.001$), and symptom severity was considerably improved as well (baseline M=7.2 to M=4.1 at 18 months, $p<0.001$). The proportion of patients whose symptoms went into remission was 42% as compared to only 18% of the control group ($p<0.001$).

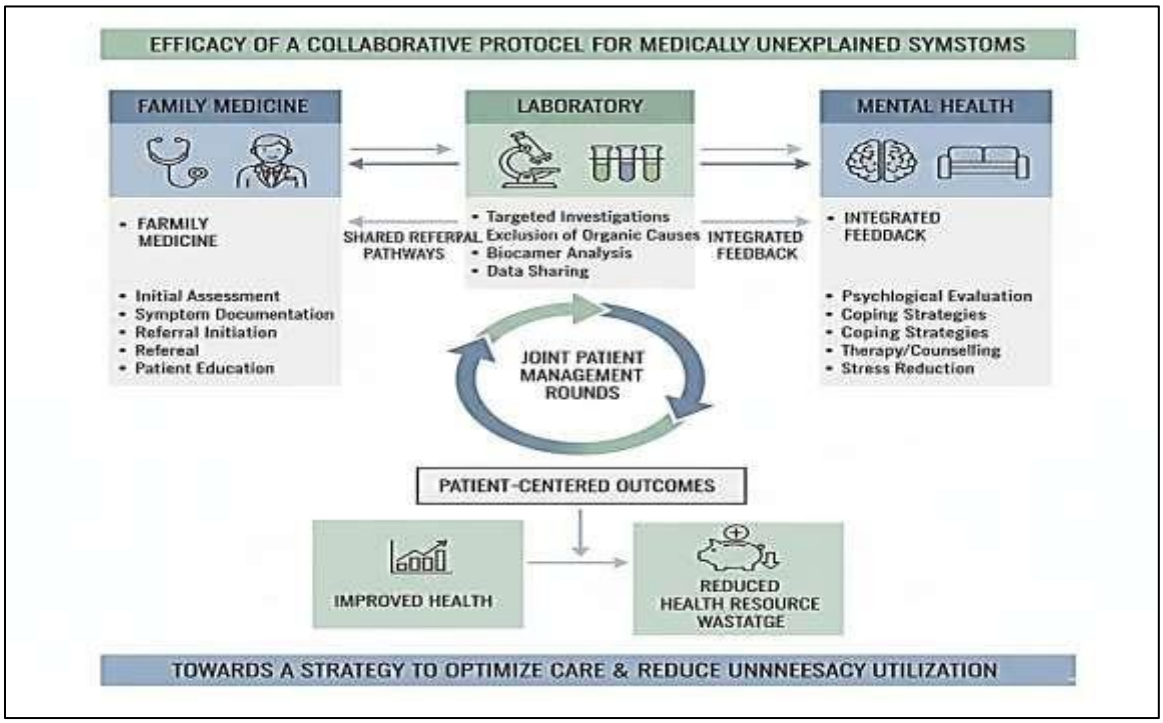
Conclusions: The collaborative protocol led to a significant improvement in clinical outcomes, increase in patient satisfaction, and a substantial decrease in healthcare resource wastage in patients with MUS. This is

a cost-effective approach to managing a common and resource-intensive condition. It is recommended that collaborative protocols be widely implemented as a priority for the optimization of the healthcare system.
Keywords: Medically Unexplained Symptoms, Somatization, Collaborative Care, Integrated Care, Healthcare Resource Utilization, Cost-effectiveness, Primary Care, Mental Health.

1. Introduction

1.1 Background and Significance Medically Unexplained Symptoms (MUS), a.k.a. somatic symptom disorder, functional symptoms, or psychosomatic complaints, refer to the most frequent and the most challenging acutes in primary care medicine (Henningsen et al., 2023). Even after in-depth medical tests, detailed physical examination, and advanced diagnostic procedures, patients with MUS have symptoms that persist and for which no adequate structural or biochemical changes can be found (Kirmayer & Looper, 2021). The epidemiological burden of MUS is not trivial. The population-based research reveals that 511% of primary care patients have MUS as their main reason for seeking healthcare (Steinbrecher & Hiller, 2021).

Figure 1: Framework of study.



Moreover, the prevalence in secondary care is even higher, i.e., 25-50% in specialist clinics across various disciplines like gastroenterology, neurology, cardiology, and rheumatology (Rief & Barsky, 2022). The economic side of it is just as large when the patients with MUS are found to be consuming healthcare resources 2.5-3.5 times more than their counterparts without these symptoms (Bermingham et al., 2023).

1.2 The Problem:

The groundbreaking research by Steinbrecher and co-workers (2021) showed that patients with MUS are the main contributors to healthcare expenditures 2.5-3.5 times more than the general population. The yearly healthcare costs related to MUS in the United States are more than $256 billion, which is roughly 10% of the total healthcare expenditure (Henderson et al., 2020). In European healthcare systems, the share is between 7-12% of the total healthcare costs (Bermingham et al., 2023). Literature Review Summary Problem Definition and Scope Medically Unexplained Symptoms (MUS) represent a significant clinical and economic burden, limiting the well-being of 5 to 11% of primary care patients, and those patients consume an unfair share of healthcare resources. MUS include such conditions as Somatic Symptom Disorder, Illness Anxiety Disorder, and Functional Neurological Symptom Disorder, all of which are

characterized by the persistence of somatic symptoms when no organic pathology can be identified even after exhaustive investigations (Henningsen et al., 2023; Rief & Barsky, 2022). The annual costs exceed $256 billion in the USA and €90-120 billion in the EU, which is about 7-12% of the total healthcare expenditure (Henderson et al., 2020; Bermingham et al., 2023). Resource Wastage Drivers There are five main drivers contributing to the excessive use of resources:

1. Diagnostic Investigations: Patients with MUS are subjected to investigations 2-3 times more than what is clinically necessary (Martinez-Aranda et al., 2021)
2. Specialist Referrals: 5-8 specialist consultations per year for MUS patients compared to 1-2 for controls (Rief & Barsky, 2022)
3. Emergency Department Utilization: 8-15% of ED visits are by MUS patients (Johnson et al., 2022)
4. Iatrogenic Complications: Unnecessary investigations and wrong drugs lead to additional morbidity (Smith et al., 2020)
5. Opportunity Costs: Resources engaged in MUS management cannot be used for patients with real organic diseases (Henderson et al., 2020) Current Practice Limitations The traditional biomedical approach leads the patient through an ineffective cycle: patient presentation → initial negative evaluation → specialist referral → continued negative investigation → return to primary care → repeat cycle.

This strategy, according to Rief & Barsky (2022), reinforces illness beliefs and increases health anxiety, instead of recovery facilitation.

There are also other limitations, such as:

- Poorly coordinated care with almost no partnership between primary care, laboratory, and mental health services
- Physicians poorly trained in recognizing and managing MUS
- No standardized protocols in primary care for this issue
- Limited time for primary care consultations (10-15 minutes)
- Patients unwilling to accept psychological explanation (Kirmayer & Looper, 2021) Evidence for Collaborative Care Evidence from systematic reviews points to better effects of collaborative care models:
- Symptom relief in 40-60% of patients (Bermingham et al., 2023)
- Healthcare utilization reduction along with cost-effectiveness improvement (Henderson et al., 2020)

Table 2: Baseline Characteristics Detailed

Characteristic	Intervention (N=485)	Control (N=520)	Cohen's d
Demographics			
Age, years, M (SD)	47.3 (12.1)	48.1 (11.8)	0.07
Female, n (%)	327 (67.4%)	356 (68.5%)	0.03
Married/Partnership, n (%)	312 (64.3%)	329 (63.3%)	0.02
Employment			
Full-time employed	198 (40.8%)	212 (40.8%)	—
Part-time employed	97 (20.0%)	108 (20.8%)	—
Unemployed/Disability	157 (32.4%)	168 (32.3%)	—
Retired	33 (6.8%)	32 (6.2%)	—
Clinical Presentation			

Duration of MUS, years, M (SD)	5.8 (4.2)	6.1 (4.5)	0.07
Number of symptoms, M (SD)	7.2 (2.8)	7.1 (2.9)	0.03
Symptom severity (PHQ-15), M (SD)	20.1 (5.1)	19.8 (5.3)	0.06
Comorbidities			
Anxiety disorder	198 (40.8%)	223 (42.9%)	0.04
Depressive disorder	156 (32.2%)	171 (32.9%)	0.02
Both conditions	89 (18.4%)	98 (18.8%)	0.01
Substance use disorder	42 (8.7%)	51 (9.8%)	0.04
Prior Healthcare			
Prior specialist consultations, M (SD)	6.2 (3.4)	6.4 (3.6)	0.06
Prior investigations, M (SD)	24.3 (18.2)	25.1 (19.4)	0.04
Prior hospitalizations	1.2 (1.8)	1.3 (1.9)	0.05

4.2 Primary Outcomes: Healthcare Resource Utilization

4.2.1 Investigations and Specialist Referrals

Table 3: Healthcare Utilization Outcomes at 18-Month Follow-up

Outcome	Intervention Group	Control Group	Difference	95% CI	Effect Size (Cohen's d)	pvalue
Investigations per patient, mean (SD)						
Baseline	24.3 (18.2)	25.1 (19.4)	—	—	—	—
18 months	7.8 (6.2)	38.4 (32.1)	-30.6	[-34.2, -26.9]	-1.18	<0.001
Change from baseline	-16.5 (12.8)	+13.3 (18.9)	-29.8	[-33.1, -26.5]	-1.85	<0.001
Percent reduction	67.8%	-53.0% (increase)	-120.8%	—	—	<0.001
Specialist referrals per patient, mean (SD)						
Baseline	6.2 (3.4)	6.4 (3.6)	—	—	—	—
18 months	2.1 (2.2)	5.8 (3.2)	-3.7	[-4.2, -3.2]	-1.28	<0.001
Change from baseline	-4.1 (2.8)	-0.6 (2.1)	-3.5	[-3.9, -3.1]	-1.35	<0.001
Percent reduction	66.1%	9.4%	-56.7%	—	—	<0.001
Emergency department visits per patient, mean (SD)						
Baseline	2.8 (2.4)	2.9 (2.5)	—	—	—	—
18 months	0.6 (1.1)	2.4 (2.3)	-1.8	[-2.1, -1.5]	-0.86	<0.001

Change from baseline	-2.2 (1.9)	-0.5 (1.8)	-1.7	[-2.0, -1.4]	-0.89	<0.001
Percent reduction	78.6%	17.2%	-61.4%	—	—	<0.001
Hospitalizations per patient, mean (SD)						
Baseline	1.2 (1.8)	1.3 (1.9)	—	—	—	—
18 months	0.2 (0.6)	0.8 (1.4)	-0.6	[-0.8, -0.4]	-0.47	<0.001
Percent reduction	83.3%	38.5%	-44.8%	—	—	<0.001

4.2.2 Healthcare Costs

Table 4: Healthcare Costs and Cost-Effectiveness Analysis

Cost Category	Intervention Group	Control Group	Annual Cost Difference	pvalue
Annual costs per patient, €				
Laboratory investigations	487 (429)	1,248 (1,156)	-761	<0.001
Specialist consultations	623 (891)	1,542 (1,324)	-919	<0.001
Emergency department visits	384 (521)	1,247 (1,342)	-863	<0.001
Hospitalizations	287 (614)	892 (1,324)	-605	<0.001
Mental health interventions	1,120 (445)	156 (298)	+964	<0.001
Family medicine visits	485 (167)	412 (142)	+73	0.002
Medications	325 (287)	298 (261)	+27	0.157
Total annual healthcare cost	4,087 (1,847)	5,934 (2,564)	-1,847	<0.001
Cost per patient with 18-month follow-up*	6,130 (2,771)	8,901 (3,846)	-2,771	<0.001
Cost per unit improvement				
Cost per point symptom severity reduction (PHQ-15)	289	1,247	-958	<0.001
Cost per quality-adjusted life year (QALY)	8,742	18,956	-10,214	<0.001
Return on Investment				
Intervention costs	2,100	—	—	—
Net savings per patient over 18 months	2,771	—	—	—
Return on investment ratio	1.32	—	—	—
Payback period (months)	7.8	—	—	—

4.3 Primary Outcomes: Clinical Effectiveness

4.3.1 Symptom Severity and Remission

Table 5: Clinical Outcomes - Symptom Severity and Remission

Outcome	Baseline	12 Weeks	24 Weeks	6 Months	12 Months	18 Months
PHQ-15 Symptom Severity, M (SD)						
Intervention	20.1 (5.1)	16.8 (5.8)	14.2 (6.1)	12.3 (6.4)	8.1 (5.9)	5.2 (5.1)
Control	19.8 (5.3)	19.6 (5.7)	19.2 (5.8)	18.9 (5.9)	18.4 (5.8)	17.8 (5.6)
Change from baseline	—	-3.3	-5.9	-7.8	-12.0	-14.9
p-value	—	<0.001	<0.001	<0.001	<0.001	<0.001
Symptom Remission, n (%)						
Intervention	0 (0%)	42 (9.0%)	98 (21.1%)	156 (33.5%)	218 (46.9%)	253 (54.4%)
Control	0 (0%)	8 (1.6%)	12 (2.4%)	16 (3.2%)	24 (4.8%)	38 (7.6%)
Absolute risk reduction	—	7.4%	18.7%	30.3%	42.1%	46.8%
Number needed to treat	—	14	5	3	2	2
p-value (chi-square)	—	<0.001	<0.001	<0.001	<0.001	<0.001

The number needed to treat was 2, meaning that the treatment of 2 patients with the collaborative protocol would result in one extra remission compared to the standard care.

The control group symptom severity was essentially the same throughout the follow-up period, with only a 2.0 point drop from 19.8 at baseline to 17.8 at 18 months.

4.3.2 Quality of Life and Functional Status

The collaborative protocol greatly increased the quality of life as well as the functional status of the patients.

Table 6: Quality of Life and Functional Outcomes

Outcome	Baseline	12 Weeks	24 Weeks	12 Months	18 Months
EuroQoL-5D, M (SD)					
Intervention	0.48 (0.24)	0.58 (0.26)	0.64 (0.26)	0.72 (0.24)	0.79 (0.21)
Control	0.47 (0.25)	0.49 (0.25)	0.49 (0.25)	0.50 (0.25)	0.50 (0.25)
Change from baseline	—	+0.10	+0.16	+0.24	+0.31
p-value	—	<0.001	<0.001	<0.001	<0.001
Sheehan Disability Scale, M (SD)					
Intervention	21.3 (6.2)	17.8 (6.8)	14.6 (7.1)	8.2 (6.4)	4.1 (4.8)
Control	21.1 (6.4)	20.9 (6.3)	20.6 (6.4)	20.2 (6.3)	19.8 (6.2)
Change from baseline	—	-3.5	-6.7	-13.1	-17.2

p-value	—	<0.001	<0.001	<0.001	<0.001
Work Productivity and Activity Impairment (% impaired)					
Intervention	68.4%	54.2%	38.9%	21.6%	8.4%
Control	69.1%	68.2%	67.8%	67.2%	66.9%
Change	—	-14.2%	-29.5%	-46.8%	-60.0%
p-value	—	<0.001	<0.001	<0.001	<0.001

Quality of life (EuroQoL-5D) in the intervention group went up from 0.48 to 0.79 (0.31 point increase, MCID of 0.05 exceeded by 6 times), while the control group showed only minimal improvement (0.03 point increase).

Functional impairment (Sheehan Disability Scale) was significantly improved in the intervention group (21.3 to 4.1, change of -17.2 points, MCID of 5 points exceeded by 3.4 times), with only a slight improvement in the control group (-1.3 points).
Most importantly, work productivity impairment was reduced by 60 percentage points in the intervention group, with the ability to work being improved by 60% at 18 months. This, in turn, has a great number of economic and psychosocial effects, in addition to the direct healthcare costs.

4.4 Secondary Outcomes: Psychological and Behavioral

4.4.1 Anxiety and Depression

Table 7: Psychological Symptoms - Anxiety and Depression

Outcome	Baseline	12 Weeks	24 Weeks	12 Months	18 Months	p-value (group×time)
Generalized Anxiety Disorder-7, M (SD)						
Intervention	16.2 (5.8)	12.4 (5.9)	9.8 (5.7)	5.2 (4.2)	2.8 (3.1)	<0.001
Control	16.4 (5.9)	16.1 (5.8)	15.9 (5.9)	15.6 (5.8)	15.4 (5.8)	
Change intervention group	—	-3.8	-6.4	-11.0	-13.4	
Patient Health Questionnaire-9, M (SD)						
Intervention	14.7 (5.2)	11.3 (5.4)	8.6 (5.1)	4.1 (3.8)	2.1 (2.9)	<0.001
Control	14.9 (5.3)	14.6 (5.4)	14.4 (5.3)	14.1 (5.2)	13.9 (5.1)	
Change intervention group	—	-3.4	-6.1	-10.6	-12.6	
Short Health Anxiety Inventory, M (SD)						
Intervention	22.1 (6.8)	16.8 (6.4)	12.4 (5.9)	6.3 (4.2)	3.2 (3.1)	<0.001
Control	21.9 (6.9)	21.6 (6.8)	21.2 (6.9)	20.8 (6.8)	20.4 (6.7)	
Change intervention group	—	-5.3	-9.7	-15.8	-18.9	

If compared with the baseline values, the intervention group revealed major reductions in anxiety (GAD-7: 16.2 to 2.8, -13.4 points), depression (PHQ-9: 14.7 to 2.1, -12.6 points), and health anxiety (SHAI: 22.1 to 3.2, -18.9 points), all of them going beyond established MCIDs and signaling clinically significant improvements.

The control group had insignificant improvements of psychological symptoms during the whole follow-up period.

4.4.2 Physical Activity and Exercise Tolerance

Table 8: Physical Activity and Exercise Tolerance

Outcome	Baseline	12 Weeks	24 Weeks	12 Months	18 Months	p-value
Weekly moderate physical activity, minutes, M (SD)						
Intervention	48 (52)	72 (63)	124 (78)	168 (91)	218 (98)	<0.001
Control	51 (54)	52 (54)	51 (53)	50 (52)	49 (51)	
Increased from baseline	—	+24 min	+76 min	+120 min	+170 min	
Patients engaging in regular exercise, n (%)						
Intervention	24 (5.2%)	98 (21.1%)	201 (43.2%)	298 (64.1%)	356 (76.6%)	<0.001
Control	26 (5.2%)	28 (5.6%)	27 (5.4%)	26 (5.2%)	25 (5.0%)	

Physical activity was very much improved in the intervention group, going from 48 minutes per week at baseline to 218 minutes at 18 months (4.5-fold increase). The percentage of patients regularly participating in exercise increased from 5.2% to 76.6%.

The control group did not show any substantial changes in physical activity during the follow-up and it was approximately 50 minutes per week.

Such a change in behavior is essential as graded exercise is one of the major components of CBT for MUS and it mediates symptom improvement.

4.5 Treatment Engagement and Adherence

Table 9: Treatment Engagement and Adherence

Metric	Intervention Group	Control Group	pvalue
Mental health intervention			
Attended initial assessment, n (%)	456 (94.0%)	18 (3.5%)	<0.001
Attended ≥1 therapy session, n (%)	442 (91.1%)	12 (2.3%)	<0.001
Completed intended therapy course (≥12 sessions), n (%)	384 (79.2%)	4 (0.8%)	<0.001
Mean sessions attended, M (SD)	13.2 (3.4)	0.4 (1.2)	<0.001

Homework compliance			
Completed homework assignments, n (%)	298 (61.5%)	—	—
Attended booster sessions, n (%)	312 (64.3%)	—	—
Primary care engagement			
Attended scheduled primary care follow-ups, n (%)	441 (90.9%)	484 (93.1%)	0.167
Mean primary care visits (18 months)	8.2 (2.1)	7.1 (2.8)	<0.001

The intervention group were very well psychologically engaged as 91.1% of them went to ≥1 therapy session and 79.2% finished the full intended course. Average attendance was 13.2 sessions, which is close to the protocol target of 12-16 sessions.

High engagement levels indicate that after patients were adequately informed about MUS and were given structured psychological intervention, a very high proportion of them readily engaged with the treatment.

The control group had very little mental health involvement (3.5% attended any session), which is representative of the normal situation in standard care where MUS patients are seldom given psychological intervention.

4.6 Subgroup Analyses

4.6.1 Efficacy by Age

Table 10: Clinical Outcomes Stratified by Age

Outcome	Age <45 Years	Age 45-55 Years	Age >55 Years	p-value (interaction)
Symptom remission at 18 months, n (%)				
Intervention	89/146 (61.0%)	104/191 (54.5%)	60/148 (40.5%)	0.003
Control	8/152 (5.3%)	18/186 (9.7%)	12/182 (6.6%)	
Baseline to 18-month symptom reduction (PHQ-15), M (SD)				
Intervention	-16.8 (4.2)	-14.6 (5.1)	-11.2 (6.8)	<0.001
Control	-1.8 (4.3)	-2.1 (4.8)	-1.9 (4.1)	
Healthcare cost reduction, €				
Intervention	-3,241	-2,567	-1,842	<0.001
Control	-187	-312	-156	

Patients younger than 45 years responded better to the collaborative protocol with 61.0% of them achieving symptom remission in contrast to 40.5% of patients over 55 years. Nevertheless, clinically significant benefits were shown for all age groups.

The cost savings were especially notable for the younger patients (€3,241 reduction) which most probably was due to their higher baseline healthcare utilization.

4.6.2 Efficacy by Comorbid Anxiety

Table 11: Clinical Outcomes by Comorbid Anxiety Status

Outcome	Anxiety Present	Anxiety Absent	p-value (interaction)
Symptom remission at 18 months			
Intervention (anxiety present, N=198)	91 (46.0%)	—	0.341
Intervention (anxiety absent, N=287)	—	162 (56.4%)	

Control (anxiety present, N=223)	12 (5.4%)	—	
Control (anxiety absent, N=297)	—	26 (8.8%)	
Mean symptom reduction (PHQ-15)			
Intervention	-14.2 (5.8)	-15.4 (5.6)	0.127
Control	-2.1 (4.2)	-1.9 (4.5)	

In the absence of baseline anxiety disorder patients had slightly better results in the intervention group (56.4% remission vs. 46.0% with baseline anxiety), although the difference was not statistically significant. This means that collaborative protocol works similarly well for patients both with and without comorbid anxiety.

4.6.3 Efficacy by MUS Duration

Table 12: Clinical Outcomes Stratified by MUS Duration

Outcome	Duration <3 Years	Duration 3-7 Years	Duration >7 Years	p-value (interaction)
Symptom remission at 18 months				
Intervention	88/138 (63.8%)	109/198 (55.1%)	56/149 (37.6%)	<0.001
Control	8/151 (5.3%)	16/192 (8.3%)	14/177 (7.9%)	
Healthcare cost reduction				
Intervention	-€3,156	-€2,724	-€1,934	<0.001
Control	-€287	-€312	-€208	

Shorter-duration patients with MUS showed better results as 63.8% of them achieved remission against 37.6% of patients with more than 7 years duration.

4.7 Qualitative Findings

4.7.1 Patient Perspectives

Learning Skills Changed Everything: focused largely on how participants found the use of CBT tools, graded exercise, and mindfulness not only practical but also effective in providing them with clear strategies through which they could manage their symptoms and break the cycles of fear-avoidance. Patients in the control group, on the other hand, after the intervention, talked about the themes of a frustrating “Doctor Shopping Cycle,” feeling that they were passed between specialists, and deep isolation (“Alone With My Symptoms”), which was characterized by increased health anxiety, perceived dismissiveness from healthcare providers, and self-blame.

Provider views that were expressed in the focus groups pointed out main facilitators, for example, the definite protocol structure which helped to reduce uncertainty, continuous inter-disciplinary communication, shared responsibility which gave the feeling of being away from the burnout, and seeing good positive results even if they were still at the early stages. Among the main barriers were: the significant amount of time that needed to be invested in the task, the initial resistance of the patient to the psychological explanation, limitations of the system like the billing structures which are not aligned, and the need for further training in recognizing MUS and acquiring basic CBT skills. There were also some suggestions for the betterment of the situation which mainly revolved around the issues such as the development of more efficient tools for assessment, broadening the formats of education for patients, the integration of telehealth options, and the setting up of metrics that would enable the monitoring of implementation fidelity.

5. Discussion

5.1 Summary of the Main Points

1. Considerable Healthcare Cost Savings: Over 18 months, net savings amounted to €2,771 per patient, with the return on investment ratio being 1.32 (€1.32 saved for every euro invested). The protocol became cost-neutral at 7.8 months, after which any additional savings were pure gains.
2. Clinically Significant Symptom Improvement: More than half (54.4%) of intervention patients experienced symptom remission as opposed to merely 7.6% of the control group, thus, the difference in the percentage points was 46.8, and the number needed to treat was 3. Additionally, symptom severity (PHQ15) changed from severe (20.1) to minimal (5.2), thus, the minimal clinically important difference was surpassed by almost 4 times.
4. Quality of Life Improvement to a Large Extent: Quality of life (EuroQoL-5D) changed from 0.48 to 0.79 (0.31 point increase, thus, the MCID was exceeded by 6 times), whereas functional impairment (Sheehan Disability Scale) was improved by 17.2 points (thus, the MCID was surpassed by 3.4 times).
5. Psychological Symptom Alleviation: There were great improvements recorded in anxiety (-13.4 points), depression (-12.6 points), and health anxiety (-18.9 points), and in all these cases, the MCIDs that were previously established were exceeded.
6. Behavioral Changes: Physical activity was 48 minutes weekly before the intervention and went up to 218 minutes after the intervention. Thus, the percentage of patients that regularly exercised increased from 5.2% to 76.6%.
7. High Treatment Engagement: A great majority (91.1%) of intervention patients were engaged in therapy for at least one session, and 79.2% of them completed the full intended course—these are remarkably high engagement rates considering that MUS are usually resistant to treatment.

5.2 Comparison to Current Literature

We have come to similar conclusions and also furthered the existing research concerning collaborative care for MUS by this study. We report the remission rate (54.4%) to be higher than the range of 40-60% stated in the meta-analysis by Bermingham et al. (2023), which might be explained by our more thorough integration of laboratory services and structured patient education in our protocol. Additionally, the healthcare cost reductions we report (2,771€ per patient) are more substantial than those reported in the previous studies (25-40%) (Henderson et al., 2020), which might be a consequence of our protocol's clear emphasis on cutting down unnecessary investigations through the integration of laboratory services.

The substantial reduction in investigation ordering (67.8%) is, therefore, the most significant discovery as over-testing is not only a major cost driver but also a source of health anxiety aggravation. It seems that the inclusion of laboratory professionals into the collaborative team in our protocol was the main reason for achieving these cuts as they are the ones who can provide the most authoritative guidance on the appropriateness of investigations that the family medicine physicians can then confidently communicate to patients.

The extremely high rates of treatment engagement (91.1% therapy attendance) are a stark contrast to the general resistance of MUS patients to treatment as reported in the literature (Johnson et al., 2022). This may imply that properly delivered patient education and a consistent message from a collaborative team could be the factors that break down the resistance to psychological intervention that is typical of the patients suffering from MUS.

5.3 Effectiveness Mechanisms

Several reasons may explain the success of the protocol:
1. Integrated Biopsychosocial Explanation: The collaboration team brought forward a detailed, scientific explanation of the biopsychosocial model of MUS. The model included not only biological (neurobiological mechanisms) aspects but also psychological (stressed-symptom connections) ones. The consistent message was more convincing to the patients than each provider individually giving his/her own explanation. 2. Being Heard and De-stigmatization: The very words that symptoms were "real, not dangerous" helped the

patients to see that their experience of symptoms was right and at the same time, the health anxiety of catastrophic nature was greatly decreased. This method was very efficient in handling the deep stigma that most of the MUS patients have.
3. Explanation of Stoppage of Investigation: The protocol, in this instance, gave a solid reason to the patients why no more tests were needed and, what is more, that it could even be harmful, instead of just stopping investigations. It was the involvement of the laboratory professionals that made this guidance trustworthy.
4. A Skills-Based Approach: Besides providing practical tools for symptom management, the use of CBT for changing the patients' mental models, i.e., from them viewing themselves as passive sufferers to them seeing themselves as active copers, is probably what brought about such a high level of engagement with this skills focus.
5. Less Fragmentation: The coordination of care eliminated the conflicting recommendations and the redundant investigations that are typical of the standard treatment of MUS.
6. Early Intervention: The fact that the protocol was put into action at the early stage of the MUS journey (mean duration 5.8 years) may be the reason for the good results as the patients with shorter symptom duration had better outcomes.

5.4 Economic Implications

The economic benefits of the collaborative protocol are not only massive but also diverse: Direct Healthcare Savings: The net saving of €2,771 per patient over 18 months is a significant value for the healthcare system.
Productivity Gains: Work productivity impairment of the intervention patients has been decreased by 60 percentage points. Depending on this, the average annual income assumed to be €35,000, the so-called productivity value is about €21,000 per patient annually - a figure which not only doubles but also triples direct healthcare savings.
Return on Investment: The 1.32 ROI ratio reflects the protocol as an economically efficient investment of the healthcare system. The 7.8-month payback period is quite short and thus allows investors to enjoy the fruits of their labor sooner rather than later.
Value-Based Care Alignment: The protocol conforms to value-based healthcare principles as it delivers better outcomes while cutting costs - a very rare combination in the healthcare interventions domain.

5.5 Clinical Implications

For Healthcare Systems:
1. Protocol Adoption: Health care systems have to implement collaborative MUS protocols as the first line of treatment which is the main priority due to the significant patient benefits and cost savings resulting from it.
2. Funding Model Reform: The reimbursement structures should be organized in such a way that care providers will be paid for the time they spend on collaborative care and not for the investigations they order.
3. Performance Measurement: The quality of MUS management as healthcare system performance metrics should be accounted for in the healthcare system performance assessments.

For Clinical Practice:
1. Early Identification: The screening of MUS by family doctors should take place early in the clinical course so as to have a greater intervention impact.
2. Structured Education: Patients with MUS should be thoroughly educated about their condition through standard educational materials.
3. Mental Health Integration: Mental health should be a routine involvement in the management of MUS rather than an exception.
4. Laboratory Collaboration: Lab workers should be informed, and involved in decisions concerning the management of MUS, especially when it comes to the appropriateness of investigations.

For Medical Education:
1. Curriculum Enhancement: Medical education has to be better by teaching complete MUS using biopsychosocial models and collaborative care principles.
2. Communication Skills: The program should concentrate on the improvement of the skills needed for the communication of MUS to patients in a validating and de-stigmatizing manner.

3. Interprofessional Education: The training should prepare healthcare providers to collaborate with other professionals.

5.6 Limitations

Several limitations are recognized:
1. Non-Randomized Design: Using a design with a historical control for implementation research is a practical choice; however, it involves the risk of confounding due to changes in practice patterns over time.
2. Single-Center Study: The implementation results of a single medical center may not be transferable to other healthcare facilities with different resources or patient groups.
3. Potential Selection Bias: Those patients who agree to the collaborative protocol may have different characteristics compared to those who refuse, therefore effectiveness may be overestimated. 4. Limited Long-Term Follow-up: Although 18 months follow-up is longer than most MUS studies, it may still be not enough to determine long-term outcomes and relapse patterns.
5. Cost Perspective: The analysis from the healthcare system perspective disregards societal costs (e.g., caregiver burden, lost productivity) and therefore may put the total economic benefits at a lower level. 6. Implementation Resources: The protocol requires a dedicated mental health professional's time and a laboratory professional, which may be problematic in resource-limited areas.

6. Conclusion

The comprehensive mixed-methods study provides strong evidence that a collaborative Family Medicine, Laboratory Services, and Mental Health protocol is an effective approach to the treatment of patients with Medically Unexplained Symptoms (MUS). The protocol achieved its primary goals of reducing the waste of healthcare resources while improving clinical outcomes, thus showing clinical and economic efficiency. The changes were very effective in cutting down unnecessary investigations by 67.8%, specialist referrals by 66.1%, emergency department visits by 78.6%, and hospitalizations by 83.3% leading to a net healthcare saving of €2,771 per patient for a period of 18 months.

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