11 Patient-Centered Outcomes Research and Collaborative Evidence-Based Medical and Dental Practice for Patients with Temporomandibular Joint Disorders

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Abbreviations

EBD	Evidence-based dentistry
EBDM	Evidence-based clinical decision-making
EBrCPGs	Evidence-based revisions of clinical practice guidelines
fMRI	Functional magnetic resonance imaging
PCOE	Patient-centered outcomes evaluation
TMD	Temporomandibular joint disorders
TMJ	Temporomandibular joint
WHO	World Health Organization

Core Message

The novel discipline of research synthesis and translational effectiveness pioneers a fresh conceptualization of clinical practice in dentistry in the context of translational science that is grounded on the pursuit and the utilization of the best available evidence. This chapter examines specific facets of this novel model of evidence-based clinical decision-making (EBDM) in health care in general and in evidence-based dentistry (EBD) in particular and specifically for patients with temporomandibular joint disorders (TMD).

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11.1 The Temporomandibular Joint

The body is endowed with two temporomandibular joints (TMJ): one on the right and the other on the left of the facial skeleton. The TMJs are the dual articulation of the mandible with the maxillary bone of the frontal aspect of the skull. The TMJs are ginglymoarthrodial joints in that they

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consist of a hinge-type joint (i.e., ginglymal[1]) and a sliding arthrodial[2] component [1].

The joint itself is encapsulated by a fibrous tissue and is composed of the condylar process of the mandible below and the glenoid fossa (i.e., the articular face) of the temporal bone above. Between these articular surfaces lies a biconcave, transversely oval disc composed of dense fibrous connective tissue referred to as the articular disc, also called the meniscus. Tight fibers connect the mandible to the disc from below, whereas looser fibers hold the meniscus to the temporal bone superiorly. This anatomical distinction results in the property of the temporomandibular joint consisting of two distinct capsules, an upper and a lower joint space, that are separated by the meniscal disc. A synovial membrane lines the inner facet of this fibrous capsule apart from the articular surfaces and the disc and secretes temporomandibular synovium,[3] which fills and lubricates the upper and lower spaces and distributes essential growth factors, cytokines, and nutrients to the tissues within the joint.

The meniscus is concave, which produces an anterior band, an intermediate zone, and a posterior band. Posterior to the disc is loose vascular tissue termed the bilaminar region. It is a relatively loose tissue that sits posterior to the articular disc and that is rich in vascularization. It provides posterior attachment of the meniscus and extensive blood and lymph circulation.

The movement of the joint has two phases:

- When the mouth is first opened, the initial movement of the mandibular condyle is rotational and involves primarily the lower joint space.
- When the mouth is opened further, the movement of the condyle is translational and involves the upper joint space.

The overall translational movement of the temporomandibular joint therefore is obtained by a sliding downward motion of the condylar head along the articular eminence, which constitutes the front border of the articular fossa. The articular eminence prevents and limits the excessive forward movement of the condyle and is aided in this function by the stylomandibular and the sphenomandibular ligament that are not directly associated with the joint capsule as well as the temporomandibular ligament (i.e., lateral ligament), which is the lateral extension of the fibrous capsule itself. The movement of the joint acts similar to a pump, such that circulation is particularly increased when the head of the condyle translates down the articular eminence.[4]

The regulation of TMJ movements—that is to say, the opening and closing of the mouth—is directed by the muscles of mastication. Therefore, TMD is often taken as an umbrella term that describes dysfunction of the masticatory musculature,[5] which can severely impair TMJ movement, and eventually its anatomy. Because of its anatomical architecture, the resting position of the joint is determined by occlusion principles—that is, how the upper teeth sit upon the lower teeth when the mouth is closed. When the adequate support is not provided by the relative occlusal position of the upper and lower molars, in particular, the structure of the joint is progressively and chronically altered, which can have serious consequences on the balance of the powerful masticatory muscles.

[1]From Latin, derived from Greek, *ginglumos* for hinge.

[2]From Greek, *arthrodia* for a synovial joint which allows a gliding motion.

[3]The synovium is specialized mesenchymal tissue that facilitates the functionality of the arthrodial joints.

[4]Cf., Gray's anatomy: the anatomical basis of clinical practice. (39th ed.). Edinburgh: Elsevier Churchill Livingstone; Clemente's Anatomy: A Regional Atlas of the Human Body (6th ed., 2011). Philadelphia: Lippincott.

[5]On each side: the masseter, the temporalis (the sphenomandibularis is considered a part of the temporalis by some sources and a distinct muscle by others), the medial pterygoid, and the lateral pterygoid. The muscles of mastication originate in the maxilla and insert into the mandible and allow for TMJ movements during contraction. They are all derived from the first branchial arch during embryonic development and are all innervated by the mandibular (i.e., third) branch of the trigeminal cranial nerve V (V3).

Innervation of the TMJ is provided by the mandibular branch (V3) of the trigeminal nerve, the cranial nerve V. Cranial nerve V is the largest of the 12 cranial nerves that consist of three main branches, hence "trigeminus"—born three at birth—and trigeminal implies three parts. It is responsible for sensation in the face, but it also has certain motor functions such as regulating the masticatory musculature for opening and closing the jaw, as well as the tensor tympani,[6] tensor veli palatini,[7] mylohyoid,[8] and anterior belly of the digastric muscle.[9] The motor division of the trigeminal nerve is derived from the basal plate of the embryonic pons,[10] while the sensory division originates from the cranial neural crest and provides tactile, proprioceptive, and nociceptive afferents to the rostrum.

The three trigeminal branches originate from the trigeminal ganglion,[11] which sits in Meckel's cave[12] and contains the cell bodies of incoming sensory nerve fibers. Whence, a single large sensory root enters the brainstem at the level of pons, and, adjacent, the smaller motor root also emerges. The motor fibers are functionally distinct from sensory nerves. Thus, the mandibular branch of the trigeminal nerve, V3, is said to have general somatic afferent (sensory) components and special visceral efferent (motor) components, the latter is responsible for controlling the muscles[13] of mastication and of swallowing. These muscles have bilateral cortical representation, meaning that any unilateral pathology, arising from neural lesion (e.g., a stroke) or inflammation, is likely to cause unilateral deficits on one side of the TMJ and by compensatory action on the other side: the net result often being deficits that are observable[14] by dentists with special interest of the TMJ.

The main trigeminal nucleus in the pons is anatomically adjacent to the entry site of cranial nerve V. From this nucleus, secondary fibers cross the midline and ascend in the trigeminal lemniscus to the contralateral thalamus. The trigeminal lemniscus runs parallel to the medial lemniscus, which carries touch/position information from the rest of the body to the thalamus. Information from V3 is represented bilaterally in the thalamus[15] and hence in the cortex. The mesencephalic trigeminal nucleus is embedded in the brainstem and regulates the symmetrical coordination of TMJ, the simultaneous actions of both sides of the body, which need essentially little conscious attention.

[6]The larger of the two muscles of the tympanic cavity responsible for dampening sounds, such as those produced by chewing.

[7]Tenses and elevates the soft palate thus protecting the nasopharynx during swallowing.

[8]Depresses the mandible and elevates the hyoid during swallowing.

[9]Elevates the hyoid during swallowing.

[10]The pons, better referred to as pons Varolii (the connection, the bridge of Varolius, because it was first described by Italian anatomist and physician to Pope Gregory XIII, Costanzo Varolio [1543–1575]), is a component of the brainstem that links the medulla oblongata to the thalamus. The pons is considered to be a critical neuroanatomical structure in that it regulates signals, through its specialized nuclei, that control a vast array of functional behaviors, including sleep, respiration, swallowing, bladder control, hearing, equilibrium and movement, taste, eye coordination, facial expressions, facial sensation, and posture. Pontine pathologies lead to difficulty with balance, walking, touch and other senses, swallowing, and speaking (cf., Pritchard and Alloway, 1999, Medical neuroscience; Gray's anatomy; Clemente's anatomy, among others).

[11]Aka semilunar ganglion, gasserian ganglion, after the Austrian anatomist Johann Lorentz Gasser (1723–1765).

[12]Named after Johann Friedrich Meckel the Elder (1724–1774).

[13]Masseter, temporalis, medial pterygoid, lateral pterygoid; and tensor veli palatini, mylohyoid, anterior belly of digastric.

[14]For example, injury to peripheral branches of V3 nerve may cause partial or total, transient, or chronic paralysis of certain muscles on TMJ, thus leading to a deviation of the jaw on that side and a compensation on the TMJ of the other side (cf., Wallenberg syndrome).

[15]The thalamus distributes information between subcortical areas and the cerebral cortex, such as sensory information from V1, V2, and V3. For this purpose, almost every sensory system has a thalamic nucleus that receives sensory signals and sends them to related primary cortical area.

11.2 Worldviews of Temporomandibular Joint Disorders (TMD)

Temporomandibular joint dysfunction (or disorder) (TMD)[16] is a complex symptom of clinically recognizable manifestations, a syndrome[17] rather than a single condition. To be clear, even though it is a generally accepted agreement among TMJ specialists that TMD can be caused by multiple factors, it is also accepted that the relative relevance of these factors to the clinical profile of TMD is still poorly understood and actually forcefully debated [2, 3]. Consequently, many treatments have been proposed, each based on one or the other particular worldview of TMD etiology, sometimes acrimoniously defended but often without the benefit of hard scientific and clinical evidence. Common treatments for TMD include adjustment of occlusal balance (e.g., splints) and masticatory muscle relaxation by means of various techniques ranging from pharmaceutical muscle relaxants, acupuncture/acupressure, and psychosocial and psycho-cognitive therapy. These three forms of myotherapy are often supplemented with analgesics and other forms of pain control intervention.

It is interesting to note that there are two principal national organizations for orofacial pain related to TMD, which each follow these fundamentally distinct conceptualizations of TMD:

- The American Academy of Orofacial Pain (AAOP) was established in the 1980s, a time when the field of TMD treatment was disorganized and many different treatment and examination modalities were being utilized. Research focused on what the most effective treatments were for the constellation of problems associated with TMDs. The drive to determine the etiology of TMDs sought to confirm the proposed role of dental occlusion, which was based on clinical reports that established about 80% of the population had occlusal interferences but no pain. Jaw bruxing behavior was believed to be increased because of occlusal interferences and that it caused the onset of pain, although bruxism[18] can often (80–90% of the population) occur without pain. Based on those associations, it was deemed that malocclusion alone could not be the main etiologic factor for TMD. The identification of an unambiguous universal cause of TMDs is lacking. For this reason, they await future research to document TMDs etiologic significance.[19]
- The American Academy of Craniofacial Pain (AACP), established in 1985, by contrast "believes that TMD's are primarily structural in nature. They believe that TM disorders can cause headache, neck ache, shoulder ache, dizziness, equilibration problems and a myriad of symptoms that are sometimes not routinely associated with TMD." In the *Craniofacial Pain: A Handbook for*

[16] The term *temporomandibular disorder* refers to a group of similarly symptomatic conditions and thus provides a rather vague description of a state, rather than a specific syndrome or condition that affects the temporomandibular joints. Thus, the term temporomandibular joint dysfunction is described as the most common form of temporomandibular disorder. Yet, temporomandibular disorders have been defined as *a group of conditions with similar signs and symptoms that affect the temporomandibular joints, the muscles of mastication, or both*. It is also the case that TMD is distinct, albeit overlapping somewhat with related syndromes such as the temporomandibular pain and dysfunction syndrome, which is characterized by aching in the muscles of mastication, occasional brief severe pain on chewing, and associated with restricted jaw movement and clicking or popping sounds (Classification of Chronic Pain, International Association for the Study of Pain; Classification of Chronic Pain, Part II, B. Relatively Localized Syndromes of the Head and Neck; Group III: Craniofacial pain of musculoskeletal origin).

[17] A syndrome (Greek, syn, together + dromos, course, progression) describes a constellation of manifestations, clinically recognizable features, which collectively indicate or characterize a condition. These signs can occur together or in a recognized timeline.

[18] Bruxism (sleep or wake bruxism) is an oral para-functional activity where there is excessive clenching and grinding of the teeth. The etiology of bruxism is unclear: psychosocial factors may be implicated, and dopaminergic dysfunction and other central nervous system mechanisms may be involved in sleep bruxism.

[19] Cf., "Orofacial Pain Fourth Edition. Guidelines for Assessment, Diagnosis, and Management."

Assessment, Diagnosis, and Management, this approach follows in broad lines Costen's early recommendations.[20]

To be clear, TMD is an umbrella term used to describe pain and dysfunction of the muscles of mastication that control and regulate movement of the TMJ. In an early study, 31.4% of patients with TMD complaints were found to have masticatory muscle dysregulation (Group I), internal disc displacement was noted in about 15.5% of patients (Group II), and arthralgia, arthritis, and arthrosis disorders were observed in close to 13% of patients (Group III). Among all TMD patients, almost 40% manifested Axis II moderate to severe depression, and 48% showed moderate to severe nonspecific physical symptom of stress [4]. A more recent study confirmed this pattern of patient distribution, Group I (muscle disorders), 57.5%; Group II (disc displacement), 42.5% and 47.1% of the right and left joints, respectively; and Group III (arthralgia, arthrosis, arthritis), 19.5% and 23.0% of the right and left TMJ, whereas 42.5% of patients had moderate/severe depression scores and 60% moderate to severe somatization scores [5].

However, the occluding opposing molars must find appropriate position and support, lest the TMJ may be chronically imbalanced, which will lead to progressively impaired function. TMD prevalence among the young and adult populations is high, and it is estimated that TMD afflicts close to a third of the individuals in mid-adulthood (40–50 years of age), although teenage girls and women are generally more prone to develop TMD than their male counterparts [6].

The primary[21] symptoms of TMD in most patients are:

- Clicking, grating (i.e., crepitus), and popping noises at the TMJ: most often intermittent and unilateral during functional movement of the joint. Most joint sounds are due to internal derangement of the joint, which is a term used to describe instability or abnormal position of the articular disc.
- Clicking indicates that the articular disc has moved to and from a temporarily displaced position (disc displacement with reduction) to allow completion of a phase of movement of the mandible.
- Locking reflects the situation where the disc displaces and does not reduce (move back into position).
- Crepitus reveals arthritic changes in the joint and occurs at any time during mandibular movement, especially lateral movements.
- Restricted mandibular movement: Limited range of movement may lead to difficulty in eating or talking. In more severe cases, there may be locking of the jaw or stiffness in the jaw muscles and the joints. Often bilateral, these manifestations can be unilateral, resulting in asymmetry and deviation of mandibular movement.
- Pain[22]: Pain and tenderness on palpation in the muscles of mastication or of the joint itself (preauricular pain), usually aggravated by function (chewing, clenching, yawning). The pain is mostly dull or aching, poorly localized, and intermittent or constant in more severe cases. Typically unilateral, the pain can also be manifested bilaterally. TMD pain may be referred to the teeth and shoulder and may be associated with headache in the temporal, frontal, and occipital region, migraines (including ocular migraines), tension headache, and myofascial pain.

A recent systematic review established that for most patients, a disc displacement is just a pain-free, lifelong-lasting, "noisy annoyance"

[20] An older name for TMD is "Costen's syndrome," after James Bray Costen (1895–1962), who, in 1934, described disorder systematically. He suggested that malocclusion, specifically mandibular over-closure, caused TMD and involved ear symptoms, such as tinnitus, otalgia, impaired hearing, and dizziness, including as well burning sensation of the throat, tongue, and side of the nose. He recommended TMD treatment interventions involving correcting occlusion by building up the bite, thus balancing TMJ [35].

[21] Secondarily, and because of the proximity of the auriculotemporal nerve to the TMJ, symptoms involving hearing may become evident, including diminished auditory acuity (hearing loss), occasional tinnitus (ringing in the ear), and dizziness.

[22] TMD is the second most frequent cause of orofacial pain after dental pain.

from their TMJ. A disc displacement with reduction is relatively stable, pain-free, chronic, and lifelong. In a few patients, the disc loses its capacity to reduce on opening, and in even fewer cases, the loss of disc reduction follows closed lock, painful, and limited mouth opening. These symptoms may spontaneously resolve within months [7].

We also discussed TMD from the perspective of the arthrokinetic reflex [8]. A typical joint movement, including TMJ, can reflexively cause neuromuscular activation or inhibition. Clinical research and observations of patients with TMD have established the wide spectrum of the arthrokinetic reflex in TMD, mediated largely by retrograde transport from the V3 terminal branch to the joint (auriculotemporal nerve) and the central nervous system, which can contribute and exacerbate neuromuscular disorders, including, as we discuss throughout this book, Tourette's syndrome, cervical dystonia, complex regional pain syndrome, gait or balance disorders, Parkinson's disease, middle and inner ear dysfunction, impaired eye movement, sleep disturbances, pain, and related neurological symptoms. In this context, sleep is particularly important because lack of quality sleep has been associated with increased risks of several health issues including obesity, heart disease, and diabetes. Individual patient measures of sleep quality should include the patient's quality of sleep that can be assessed with a polysomnography in an experimental sleep study and confirmed with the two critical blood or salivary biomarkers, oxalic acid and diacylglycerol 36:3, whose levels decrease significantly following sleep deprivation and normalize upon sleep recovery, and functional MRI (fMRI).

Our initial studies of the overarching arthrokinetic reflex in TMD are grounded on the working hypothesis that by expanding the joint anatomical space, the arthrokinetic reflex is reduced. In the context of individual patient-centered translational research (cf., Chap. 10), a broad spectrum of clinical independent patient data can be obtained from patients diagnosed clinically, by palpation as well as imaging (X-rays, CT) with mild-severe TMD. Salivary and synovial levels of proinflammatory cytokines replicate the findings reported in the literature [9] and are found to correlate with significant impairments ($p < 0.05$) in neuropsychological testing (e.g., Brief Visuospatial Memory Test, Grooved Pegboard, Hopkins Verbal Learning Test, Stroop), polysomnography, and fMRI, in the state of jaw joint space constriction, compared to when the joint space is expanded [8].

TMD is very common, as 20–30% of the adult population between age 20 and 40 are affected to some degree. TMD has a substantially greater relative prevalence in women, compared to men.

11.3 Principles of Patient-Centered, Effectiveness-Focused, and Evidence-Based Intervention

The new model of health care is patient-centered, effectiveness-focused, and evidence-based [9, 10]. The depth of meaning of this statement is still only barely understood. It is fair to say that its fundamental root can be traced several centuries back, perhaps as far as Aristotelian philosophy, as we discussed elsewhere [9, 10]. In the modern era, we recall the observation of the Marquis de Vauvenargues to the effect that it is in fact easier to state concepts anew than to reconcile statements made previously by others.[23] Seeking a consensus of the evidence is often a more complex process than obtaining new evidence. That is precisely the purpose and ultimate goal of the research design of the research synthesis model in evidence-based health care: to reconcile research evidence toward obtaining the best available evidence (evidence-based) for effective and efficacious treatment intervention (effectiveness-focused) for addressing clinical issues in specific patients (patient-centered).

The position that holds the ideology that the Western approach to delivering health care is

[23] Luc de Clapiers, Marquis de Vauvenargues (1715–1747), *Réflexions et Maximes* "…il est. plus aisé de dire des choses nouvelles que de concilier celles qui ont étés dites…."

superior because it rests on research evidence is, in and of itself, a fallacy simply because it ignores[24] the self-evident fact that there is good research evidence and there is bad research evidence. If research evidence is tainted by a suboptimal research methodology, if bias and error abound, if data is mis-analyzed and misinterpreted, then it is possible and even probable that the utilization and integration of that evidence in the clinical decision-making process will be unacceptable for safe utilization in patient care.

That, in and of itself, seems self-evident and routine. But in fact, it is a typical case of onus probandi[25]—that is to say, the complex process of research synthesis engages a series of articulated steps that lead to sophisticated statistical analysis and inference, which together build the case for or against the acceptability of the best available research evidence for patient care. The burden of proof for the elaboration of the consensus of the best available evidence rests squarely on research synthesis. That is the reason why it is critically important that research synthesis be a hypothesis-driven endeavor anchored in the reliable, valid, and unbiased scientific process.

The medical literature is gargantuan. We could not exhaustively peruse the published reports in the manner just outlined, even if we had the expertise to do so, and still have the material time to take care of our patients. Therefore, we would become selective on which report we are going to peruse. By doing so, inevitably, we insert into the very process the gravest fault of all research: the bias of selection. By selecting what report we shall consider in our perusal, we de facto select the kind of evidence we will be willing to utilize in the process of sharpening our skills and expertise: we de facto taint the very process of our clinical decision-making with a bias that is inappropriate because it is not related to the condition of the patient, to the intervention we are considering, or to the outcome sought. We de facto fall into one of the most dangerous fallacies of science, in which we tend to demonstrate this; well simply because of the conditions, we selected to make the case (post hoc ergo propter hoc; selection bias).

Health care based on the evidence suffers from an unalienable bias. The best available evidence emerges from a concerted process of systematically synthesizing and analyzing all the available evidence that pertains specifically to the patient under consideration, the interventions under consideration, and the clinical outcome under consideration. Thus, when the systematic process of research synthesis is applied to the entire body of the available evidence, such that the acceptable evidence can be obtained, from which a consensus of the best available evidence can be derived, evidence-based health care is procured. Evidence-based health care is the optimal and safest manner to update skills and expertise to provide effective and efficacious health care to each individual patient in a patient-centered paradigm.

In brief, evidence-based health care, therefore, entails making fully informed clinical decisions that integrate not only the patient's medical history and clinical test results but also the training of the clinician and his/her skills and expertise updated by the consensus of the best available research evidence, itself derived from a systematic process of research synthesis.

Research synthesis [11–13] follows the scientific method, which can be outlined in brief as follows:

- Statement of the hypothesis and research question
- Crafting of the research approach to test the hypothesis and answer to the research ques-

[24] Fallacy consequential to mere ignorance of the facts (*argumentum ad ignorantiam*), that is, the assumption that a claim is true (here, that all research evidence is equally acceptable for safe use on patients – note: the oath calls health-care providers to do no harm first and foremost [primum non nocere]) simply on the basis of the lack of clearly establishing that in fact that evidence is not safe to be used in patient care; in addition, fallacy consequential to mere adherence to previously held beliefs (*argumentum ad antiquitam*) (here again, that all research evidence is equally acceptable and safe for patient care) despite cutting edge protocols designed to distinguish acceptable vs. non-acceptable research evidence.

[25] "…onus probandi incumbit ei qui dicit, non ei qui negat…" the burden of proof is on the person who makes the claim, not on the person who denies it.

tion (i.e., research design, sampling issues, tools of measurement)
- Presentation of the findings and summary of the results by means of descriptive statistics
- Statistical analysis of the data
- Inferences, discussion of limitations and intervening variables, identification of future research toward further testing the hypothesis, and answering the research question in greater details

It is critical to set the question of the research at hand and to realize that a research question, when stated in the affirmative, is nothing but the study hypothesis. Thus, for instance, one could set out to test the research query of whether *orthotic intervention is an effective and efficacious in correcting TMD with internal derangement associated with TMJ inflammation and pain*.

The search for the best available evidence, which is obtained through the research synthesis design, is hypothesis-driven because it addresses a specific type of research question that is rendered by the acronym PICOTS (patient, interventions under consideration, outcomes, timeline, clinical setting). The PICOTS research questions direct the search for evidence about which intervention under consideration may, or may not, be more effective or efficacious for the particular patient population targeted in the study and in light of the specific clinical outcome of interest.

The distinction between the "effectiveness" and the "efficacy" of a clinical intervention is critical at this juncture. The US Federal Coordinating Council for Comparative Effectiveness Research Report to the President and the Congress, dated June 30, 2009, stated that *"…because it (comparative effectiveness research) …[applies]… to real-world needs and decisions faced by patients, clinicians, and other decision makers [generally including assessment of risks, costs vs. benefits]…."* By contrast, in *"… efficacy research, …the question is typically whether the treatment is efficacious [i.e., works clinically] under ideal, rather than real-world, settings …[and]….[t]he results … are … not necessarily generalizable to any given patient…."* Simply stated, whereas effectiveness pertains to risk, benefits, and cost assessment, efficacy pertains to whether or not a given clinical intervention works clinically and brings about the clinical outcome sought.

The PICOTS questions drive the process of search and analysis of the *best available* evidence by means of the research synthesis design. It defines and determines the sample of publication to be scrutinized to obtain the *available* evidence, the tools of evaluations that serve to assess the *best* evidence, the statistical analysis required to establish reliability and validity of the results, and the inference of the findings for immediate implication to clinical practice. The PICOTS question sets the criteria for deductive reasoning leading incremental progress of research in the future. In brief, it instructs and informs the creation of new knowledge obtained through systematic research driven by the scientific method to the ultimate aim—the *causa prima* (cf., Aristotelian teleology)—providing the best available treatment intervention to individual patients in the most cost- and benefit-effective manner.

The sample of a research synthesis design is obtained in a manner that is in no way different from what is done in a clinical trial, where the investigator determines and establishes beforehand what is the accessible and what is the target sample of the study. In the research synthesis design, the sample consists in the peer-reviewed and non-peer-reviewed published research literature, as well as unrecorded observations. The term "available" underscores the fact that we limit the subjects of study in a piece of research synthesis investigation, in the same manner as any other piece of research, to the accessible sample: that is to say, the accessible research literature that specifically targets the question under study. Unpublished evidence and evidence that is published in non-peer-reviewed journals are often excluded from a research synthesis design, in part, because it is exceedingly difficult to obtain these types of evidence in a valid and reliable manner. The literature available through the proceedings of scientific meetings, dissertations, and non-peer-reviewed journals, the "gray litera-

ture," is likewise often not part of the research synthesis process, because it is generally agreed that the evidence that has not been sifted through the widely accepted peer-reviewed process is likely to be fraught with issues of validity, quality, and bias, which will interfere with the research synthesis process. In brief, the research synthesis process is most often focused, otherwise indicated, on peer-reviewed literature. The search for that sample is obtained by utilizing the medical subject headings (MeSH terms) and keywords that can be derived from the PICOTS question.

Case in point, for the PICOTS question proposed above, typical keywords could be:

- (Dental, oral) orthotic
- Temporomandibular joint disorder
- Internal derangement
- Inflammation
- Pain

Of these, "orthotic device," "temporomandibular joint disorder," and temporomandibular joint" are actual MeSH words: MeSH (medical subject headings) being the vocabulary thesaurus used for indexing articles for PubMed controlled by the National Library of Medicine.

A typical search on PubMed would develop as follows:

> orthotic [All Fields] AND ("temporomandibular joint disorders"[MeSH Terms] OR ("temporomandibular"[All Fields] AND "joint"[All Fields] AND "disorders"[All Fields]) OR "temporomandibular joint disorders"[All Fields] OR ("temporomandibular"[All Fields] AND "joint"[All Fields] AND "disorder"[All Fields]) OR "temporomandibular joint disorder"[All Fields]) AND internal[All Fields] AND derangement[All Fields] AND ("inflammation"[MeSH Terms] OR "inflammation"[All Fields]) AND ("pain"[MeSH Terms] OR "pain"[All Fields]).

This search approach would yield three entries:

A. Observational Study—Imirzalioğlu P, Uçkan S, Güler N, Haberal A, Uçkan D. (Department of Prosthodontics, Baskent University, Faculty of Dentistry, Ankara, Turkey.) Synovial apoptosis in temporomandibular joint disc displacement without reduction. Oral Surgery Oral Medicine Oral Pathology Oral Radiology Endodontics. 2009 108:693–8.

> *Objective*: Our hypothesis is that increased apoptosis in synovium might contribute to temporomandibular joint (TMJ) degeneration. To investigate this, we measured soluble Fas (sFas) and nuclear matrix protein (NMP) levels in TMJ synovial fluid from patients with disc displacement without reduction as indicators of apoptosis in the synovium.
>
> Patients and Methods: Synovial fluid was obtained from 17 joints in 17 patients (11 females, 6 males; mean age, 31.5 ± 11.9 years; range, 19–55). Patients were referred to our clinic because of limited mouth opening, joint sounds, or TMJ pain. Synovial fluid obtained by arthrocentesis for therapeutic reasons was analyzed by enzyme-linked immunosorbent assays for APO-1/Fas and cell death detection (NMP).
>
> Results: We studied 12 left (71%) and 5 right (29%) joints with disc displacement without reduction. The chief complaint was pain on the affected side and limited mouth opening. Only two patients had a click in the affected joint, whereas 14 reported pain and 17 had the limited mouth opening. All patients experienced a significant ($P < .01$) increase in maximal mouth opening immediately after arthrocentesis. Mean sFas and NMP levels were 484.9 ± 466.7 pg/mL (range, 17–1501) and 29.2 ± 13.7 U/mL (range, 8–52.8), respectively.
>
> Conclusion: Considering reports that increased sFas blocks apoptosis by inhibiting binding of FasL to Fas on the cell membrane, low level of sFas in our patients' synovial fluid (compared with amounts reported in joint inflammation or degeneration) suggests vulnerability to apoptosis in patients with internal derangement.

B. Observational Study—Sato J, Segami N, Yoshitake Y, Kaneyama K, Yoshimura H, Fujimura K, Kitagawa Y. (Department of Oral and Maxillofacial Surgery, Kanazawa Medical University, Daigaku, Uchinada-machi, Kahoku-gun, Ishikawa 920–0293, Japan. jun-s@den.hokudai.ac.jp) Specific expression of substance P in synovial tissues of patients with symptomatic, non-reducing internal derangement of the temporomandibular joint: comparison with clinical findings. Br J Oral Maxillofac Surg. 2007 45:372–7.

Our aim was to find out the extent of expression of substance P in synovial tissue from the human temporomandibular joints (TMJ), with symptomatic, non-reducing internal derangement, and to investigate the relationship between substance P and clinical findings. Fifty-four joints in 54 patients were examined immunohistochemically. Specimens of synovial tissue from 10 joints in 8 subjects with habitual dislocation of the TMJ with no pain were examined as controls. Cells that stained for substance P were found mainly among the endothelial cells in the blood vessels beneath the lining cells in synovial tissues from 47 of the 54 joints (87%) with internal derangement and from 5 of the 10 control joints. The extent score of cells that stained for substance P in joints with internal derangement was significantly higher than that in controls ($p = 0.02$). The extent score of these cells did not correlate with pain in the joint or the degree of synovitis. These results suggest that substance P may have some roles in both the physiological and pathological conditions in patients with symptomatic internal derangement of the TMJ.

C. Review (French)—De Laat A. (Département d'Odontologie, Université Catholique de Leuven) [Etiologic factors in temporomandibular joint disorders and pain]. Revue Belge Medice Dentaire 1997 52:115–23.

Parallel to the construction of better classifications and the identification of subgroups of temporomandibular disorders, an important development has taken place in research concerning its etiology. The etiological factors implied in muscle problems refer to more generalized disorders as myofascial pain syndrome and fibromyalgia. The role of occlusal and articular factors has been brought down to realistic proportions, indicating a minor contribution. Similarly, doubt has arisen concerning the existence of a vicious cycle of pain/spasm/pain. With regard to internal derangement, emphasis has been put on the high prevalence in an otherwise normal population and the fluctuating character of the symptom. Also here, developments point toward constitutional and systemic factors, more than local influences. Trauma, however, seems to play an increasing role. The development of osteoarthrosis has been studied more in depth revealing local processes of inflammation, neurogenic inflammation, and the existence of specific markers, which might be important in the future. The relationship between disc derangement and the development of osteoarthrosis remains unclear.

A similar search process through Google Scholar, which uses the keywords "oral orthotic temporomandibular joint disorder internal derangement inflammation pain," yielded those 3 reports and 165 additional ones, including reviews, case reports, and other types of study, that are not suitable for incorporation in a research synthesis design, save for background and interpretative purposes. This discrepancy serves to exemplify the fact that the search for a research synthesis project is generally actualized by accessing the National Library of Medicine (PubMed-MEDLINE, www.ncbi.nlm.nih.gov/pubmed) and at least two other search engines (e.g., Cochrane, www.cochrane.org; Bandolier, www.jr2.ox.ac.uk/bandolier; Embase, www.embase.com; Center for Reviews and Dissemination, www.york.ac.uk/inst/crd; Google Scholar; etc.). The purpose of the multiple search is to ensure comprehensive inclusion of all the available literature within the confines of the inclusion/exclusion criteria dictated by the research synthesis process while, at the same time, minimizing as much as possible dangers of selection bias and systematic sampling errors. The multiple search process produces a complete and exhaustive sample of the available evidence, as it pertains specifically to the PICOTS question, and following appropriate inclusion and exclusion criteria. The outcome of the search process is termed the bibliome.

The suffix *-ome* describes a series, or collection, of objects, or entities, that harbor a distinctive commonality. For example, the collection, the totality of the genes of an organism is termed the genome. In modern and contemporary terminology in the health and life sciences, *−omes* can provide a direct descriptor of a given field or subfield. In that sense, the proteome is the complex assembly of posttranslational products (i.e., proteins) of the organism, and the interactome describes the complex sets of gene-gene, protein-protein, or protein-gene and protein-ligand interactions that are necessary to support and maintain the survival, growth, and reproduction of the organism. By extension, the bibliome is the totality of the corpus of literature that harbors the distinctive commonality of describing the specific biological phenomena under study.

The systematic computer-driven methods for storing, retrieving, organizing, and analyzing the bibliome pertain to the research approach of bibliometrics. The systematic evaluation of the level and quality of the evidence contained within the bibliome is obtained through the research design of research synthesis and is disseminated in the form of

a research report called the systematic review. The term is meant to indicate not only that is all-encompassing of the bibliome derived from PICOTS question but also that it results from a systematic science-driven process of evaluation and quantification of the evidence level and quality, supported by stringent statistical analyses and inferences.

It must not be understated that the sampling process in research synthesis—that is, the process of establishing the bibliome—suffers from the same threats and limitations as the process of sampling in other research designs (i.e., observational designs, experimental designs, randomized clinical trials). For example, the threat of selection bias adulterates the sampling process in experimental studies when sampling is driven by convenience rather than by chance. Sampling of the literature suffers likewise from selection bias, when, for instance, our evaluation capabilities (i.e., critical reading, assessment tools) fail to be all-inclusive, including such barriers as language, search engine, and library availability, among others. That is one specific facet of the publication bias.

Case in point, a systematic review was conducted to describe the evidence for a relationship between diagnoses and findings of clinical examination and diagnoses and findings of magnetic resonance imaging (MRI) examination for degenerative and inflammatory temporomandibular joint disorders. The bibliome was obtained through the National Library of Medicine (PubMed) and the Cochrane Library. The Quality Assessment of Diagnostic Accuracy Studies (*QUADAS*) tool was used to evaluate the yielded literature. A total of 23 studies were obtained. Due to vast heterogeneity in study design, clinical examination methods, and diagnostic criteria, supportive evidence for a relationship between clinical and MRI diagnoses and findings was not established. Similarly, the relationship between clinical pain and internal derangement diagnosed with MRI could not firmly establish (odds ratio was in the low range of 1.54–2.04). The relationship between pain and disc displacement without reduction (4.82) or crepitation and disc displacement without reduction showed higher ORs (4.82 and 3.71), respectively [14].

The Cochrane Group, a leading organization in establishing the methodology of systematic reviews and research synthesis, describes the publication bias as spectrum of situations that taunt the bibliome and which may be summarized into five principal situations that favor the publication of positive data, over null or negative findings:

- More likely to be published (publication access bias)
- More likely to be published rapidly (time lag bias)
- More likely to be published in English (language bias)
- More likely to be published more than once (multiple publication bias)
- More likely to be cited by others (citation bias)

It must be acknowledged that some degree of publication bias cannot be avoided simply because, as a general rule, papers that are statistically significant, whether they demonstrate clinical relevance or not, tend to be preferentially published in the scientific literature, compared to reports that demonstrate clinical relevance but fail to reach statistical significance. The problem of publication bias is inherent to our present system of scientific literature and is an unavoidable issue of the research synthesis process, which is generally discussed as a limitation of the utilization of the best available evidence in consideration of the clinical relevance of the findings, and clinical decision-making for treatment intervention or diagnosis.

The second major domain of methodology in the research synthesis designs pertains to the assessment of the level and quality of the evidence. As the sample process described above yields the *available evidence*, the assessment of the quality of the evidence uncovers the *best evidence*.

In this context, two contemporary schools of thought can be succinctly described as such:

- One proposition is that a ranking system can be arbitrarily devised to evaluate the strength

of the results of a study purely on the basis of the nature of the design—i.e., the level of the evidence.
- Another view argues that the best research is that which most strictly adheres to the fundamental tenets and standards of research methodology, design, and analysis—i.e., quality of the evidence.

The level of the evidence paradigm is insufficient to establish whether the evidence is indeed "best," because it simply assigns a rank to the individual studies, based on the nature of the design, viz., clinical trial, observational, etc. Clinical trials are ranked second highest, the top position being assigned to systematic reviews. Some attempt is made to establish the quality of individual clinical trials by means of the checklist of the consolidated standards of reporting trials (CONSORT) [15], revised in 2010 (CONSORT 10) [16]. The criteria developed to ensure the strengthening and reporting of observational studies in epidemiology is referred to as the STROBE.

The level of evidence is established on the basis of the type of study design that was used to generate the evidence under evaluation. The US Preventive Services Task Force has established the following criteria:

- *Level I*: Evidence obtained from at least one properly designed randomized controlled trial.
- *Level II-1*: Evidence obtained from well-designed controlled trials without randomization.
- *Level II-2*: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
- *Level II-3*: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.
- *Level III*: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

The UK National Health Service uses a similar system with categories labeled A, B, C, and D
- *Level A*: Consistent randomized controlled clinical trial, cohort study, with clinical decision rule validated in different populations
- *Level B*: Consistent retrospective cohort, exploratory cohort, ecological study, outcomes research, case-control study, or extrapolations from level A studies
- *Level C*: Case-series study or extrapolations from level B studies
- *Level D*: Expert opinion without explicit critical appraisal or based on physiology, bench research, or first principles

Proponents of the assessment of the level of evidence as the means to establish the "best available" evidence have improved the ranking process of research report with the strength of recommendation taxonomy (SORT). The SORT system was created to provide a simple, user-friendly system for grading the strength of diagnostic and prognostic studies but in effect may be a biased and rather cumbersome grading device yielding no or few effective and valid recommendations. In brief, SORT yields:

- Ratings (A, B, or C) for the strength of recommendation for a body of evidence
- Qualitative inferences about good or limited evidence and consistent or inconsistent evidence
- Ratings (1, 2, or 3) for the resulting ranking of studies

The Standards for Reporting of Diagnostic Accuracy (STARD) similarly seeks to establish the accuracy and completeness of reporting of studies of diagnostic accuracy, to allow readers to assess the potential for bias in the study (internal validity), and to evaluate its generalizability (external validity). The STARD statement consists of a checklist of 25 items and recommends the use of a flow diagram which describe the design of the study and the flow of patients.

Taken together, the fundamental limitation of the assessment of the level of evidence remains that research in the health sciences utilizes all the possible and available study designs. The choice of research designs must not be dictated by the

misconception that some designs are better than others. The choice of a design is driven purely by research methodology issues and concerns and reflects the optimal methodological approach to obtain a reliable and valid quantifiable answer to the research question in a manner that can withstand the rigors of statistical analysis and generate clinically relevant new knowledge. That is the call of the scientific method.

The "best available" evidence is that research evidence that emerges from the systematic process of evaluation as the most reliable and valid evidence for the simple reason that it was obtained with the strictest adherence to the very criteria and standards that define and establish the scientific process. It is that which emerges from a research methodology, design, and data analysis that answers the research question and tests the hypothesis in a scientific approach that is the most sound possible, considering the limitations, intervening variables, and possible confounders. The best evidence only emerges from the best research, and the best research only results from fulfilling the requirements of good research, as stipulated by the research process. In brief, it is that which is least biased.

The Agency for Healthcare Research and Quality (AHRQ) has established recommendations for strength (i.e., quality) of the evidence in terms of its immunity from the risk of inherent bias. For this assessment, AHRQ developed an instrument that consists of four principal domains:

(a) *Risk of bias*: the principal component in determining the strength-of-evidence (i.e., risk of bias) score and is intended to assess methodological limitations and systematic errors. Risk of bias results from issues of inappropriate design and performance of studies by the PICOTS bibliomic search. The risk of bias component assessment proceeds by, first, considering which study design is most appropriate to reduce bias for each question; second, it requires consideration of the risk of bias from available studies; and, third, it assesses the aggregate quality of studies within each major study design and integrates those assessments into an overall risk of bias score. Individual risk of bias scores can be high (elevated risk of bias lowers strength-of-evidence grade), medium, or low (low risk of bias scores raise strength-of-evidence grade).

(b) *Consistency*: related to precision of measurements and results; inconsistency refers to imprecision of results and lack of reliability of measurements and manifests as a rather large heterogeneity or variance. Consistency is best defined as the degree of similarity in the effect sizes of different studies within an evidence base and thus reflects the consistency among evidence bases. Consistency scores can be high consistency, low consistency (i.e., inconsistent), and unknown (or cannot be assessed on the basis of the data available).

(c) *Directness*: defined as whether the evidence being assessed: (a) reflects a single, direct link between the interventions of interest and the ultimate health outcome under consideration, (b) relies on multiple links in a causal chain, or (c) utilizes analytic frameworks (a priori structure planned for measurements and data analysis). By contrast, indirectness of evidence is reflective of lack of specificity. Evidence can only be scored as direct, if the evidence is based on a single link between the intervention and health outcomes, or indirect, if the evidence relies on surrogate/proxy outcomes or more than one body of evidence.

(d) *Precision*: related to consistency, such that lack of consistency refers to imprecision of results and consequentially high heterogeneity of outcomes and prohibitive variance. Precision is defined as the degree of certainty for estimate of effect with respect to a specific outcome and specifically pertains to what can evidence-based decision-makers conclude about whether one treatment is, clinically speaking, inferior, superior, or equivalent (neither inferior nor superior) to another. Precision typically considers the statistical significance for each effect estimate separately and the confidence intervals for

those effect estimates. Precision scores can be precise, when estimates allow a clinically useful evidence-based conclusion, and imprecise, when the confidence interval is so wide; it could include clinically distinct (even conflicting) conclusions.

In addition, the instruments have secondary additional domains, which include:

1. Dose-response association
2. Plausible confounders
3. Strength of association
4. Publication bias

The scores of the individual domains are combined into a single strength-of-evidence (i.e., risk of bias) score, taking scores on additional domains into account as needed. Standardized principles of scoring, such as explicit evidence-grading criteria, clearly established point system for combining ratings of each domain, qualitative consideration of the domains—that is to say, crafting of criteria to define and refine each domain—and clear documentation of all procedures aid in establishing and formalizing the process of grading the evidence.

To compare the effectiveness of splint therapy with that of minimal or no treatment in patients with TMDs, an extensive systematic review intended to examine a vast (n = 1567) bibliome obtained from MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials for studies up to and including August 2011. But a limited number (=11) were Level I studies and therefore eligible for further analysis. Quality assessment established overall moderate quality across the 11 reports indicated that splint therapy may reduce TMJ pain, but not improve function. Overall, the results of this systematic review were inconclusive due to the individual bias inherent to the bibliome [17].

With respect to evaluating the quality of systematic reviews, Shea and colleagues developed and characterized the assessment of multiple systematic reviews instrument, through a process of factor and cluster analyses of previously existing instruments for this purpose (e.g., OQAQ, Sacks' checklist, quality assessment of studies of diagnostic accuracy included in systematic reviews, QUADAS). This process resulted in the identification of 11 domains that are sine qua non of an adequate systematic review and which constitute the 11 items of the AMSTAR [18, 19]:

1. "A priori" design provided
2. Duplicate study selection and data extraction
3. Comprehensive literature search
4. Status of publication (i.e., gray literature) used as an inclusion criterion
5. List of studies (included and excluded) provided
6. Characteristics of the included studies provided
7. Scientific quality of the included studies assessed and documented
8. Scientific quality of the included studies used appropriately in formulating conclusions
9. Methods used to combine the findings of studies
10. Publication bias
11. Conflict of interest

Taken together, the principal elements of measuring the quality of the evidence lie in the fact that the tools used must be:

- Valid—assess what they are designed to assess
- Reliable—assess what they assess in a replicable manner

In our own work, we modified the original risk of bias instrument to obtain quantitative assessment, verified its criterion validity (r = 0.96, $p < 0.05$), and established its inter-rater reliability (r = 0.94, $p < 0.05$) [20]. For the same purpose, we also validate an expansion of the original GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) instrument [21] designed for grading the quality of underlying evidence and the strength of clinical recommendations and expanded to include quantifiable assessments and measures of clinical relevance [22]. A similar research tool is the AGREE[26] (Appraisal of Guidelines and Research

[26]AGREE is an instrument developed to provide a basis for defining steps in a shared development approach to

and Evaluation, Europe) measure and its update (AGREE-II) [23].

The next critical step in the pursuance of the best available evidence is the analysis of the data. Over a decade ago, it became apparent that standards must be established for the appropriate reporting of meta-analytical analyses [24], especially when these pertained to the identification of the best available evidence for health care. The original Quality of Reporting of Meta-analyses (QUOROM) statement outlines the optimal flow of presentation of the abstract, introduction, methods, results, and discussion sections of a report of a meta-analysis. They were structured and organized into 21 headings and subheadings, which had the advantage of providing a set of guidelines for investigators, but were often arduous to understand and follow for the neophytes. In a recent development, QUOROM was revised and improved and presented as the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA; prisma.org) [25]. Whereas longer and more complex than CONSORT, PRISMA consists of a 27-item checklist and a 4-phase flow diagram, which is actually more user-friendly than QUOROM. Whereas research synthesis is the structure by which the investigator obtains the systematic review, the meta-analysis is one of the protocols that the investigator will utilize judiciously to obtain one specific aspect of analysis of the data of the systematic review.

There may be instances where a meta-analysis is not needed or impossible to conduct in a given systematic review. That, in and of itself, does not diminish the value of the systematic review product and the strength of the evidence it presents.

In and of itself, meta-analysis is simply a statistical protocol, a combinatorial process of analysis that is extraordinary sensitive to several properties of the data. Two principal properties deserve to be mentioned in the context of this discussion are heterogeneity/homogeneity of outcome and data quality.

(a) Clinical outcomes, whereas they may seem to clear and crisp measurable entities, more often than not can be quantified in more than one way. The heterogeneity in outcome measure is one clear danger for the validity of any meta-analytical reasoning, because it speaks directly to what, really, are we combining together and what really are we making overall inferences about. There are statistical tests that we must run on the outcome measurements that establish whether homogeneity is verified (cf., Cochran Q and its transformation as the I^2 test)—that is to say, whether the extent of outcome measure heterogeneity is within the level of confidence and is, in fact, not statistically significant.

(b) The data pooled together into a meta-analysis be from reports that are deemed of good quality. If the data in the input are all high quality, then the variability due to residual inexplicable error will be small, and the effect, if there is one, will be apparent and clearly statistically significant. If, on the other hand, the data that are used in the meta-analysis originate from studies that are fraught with serious quality issues, then each of these sets of data will carry into the meta-analysis its contribution of residual inexplicable error, and the total overall variability will be large and negate the ability of a statistically significant overall effect to become apparent over this residual error "noise." Similarly, albeit not as dramatically, if a meta-analysis should incorporate some solid and good studies and a few studies with serious quality issues, the contribution of the former to the variability due to residual inexplicable error will be small, but the contribution of the latter to the overall error will be disproportionately large. That will, more often than not, mask a statistically significant overall effect [9, 10, 24].

For that reason, many—most, but not all—investigators argue in favor of a two-step process of data analysis for systematic reviews, which involves establishing first the quality of the

produce high-quality clinical practice guidelines revised based upon the best available evidence.

research evidence by acceptable sampling analysis and, then, based on these assessments, eliminating the studies that demonstrate excessive flaws, as determined by the score of the quality of evidence assessment tools (i.e., acceptable sampling analysis; [18, 20]). For the studies that remain, the second step involves testing for homogeneity, and if no significant heterogeneity is noted with the accepted studies, then run the meta-analysis. The forest plot thus generated has the best likelihood of evincing overall significance, if there is one to be shown.[27] Stated in statistical terms, it is necessary to perform both acceptable sampling and homogeneity analyses in order to ensure power of a meta-analysis.

11.4 Evidence-Based Revision of Clinical Practice Guidelines for Treating TMD

The consensus statement that follows these analyses must be clear statement of the clinical implication and relevance of the research synthesis and meta-synthesis. It must present clearly the strength of the clinical recommendation thusly conceptualized [26–28].

Efficacy refers to whether or not a clinical intervention tested in the context of a clinical trial yielded valid and replicable outcomes. In lay language, we might say that efficacy tells us whether the treatment "worked," and it does so because of its inherent dependence upon the effort the investigator in constructing the research project correctly and fractionating as much as the random error as possible. In that regard, efficacy establishes the replicability of the clinical outcome. By contrast, effectiveness relates to the experiential reality of the clinical practice and pertains to whether or not the intervention minimizes risk, maximizes benefit, and yields these outcomes at the lowest (or at least the most reasonable) cost. It is fair to say that effectiveness does not pertain to a clinical trial study per se, but rather to the pragmatic implementations of its findings to the intricate complexities of clinical treatment. Careful consideration of effectiveness seeks to evaluate costs, benefits, and harms of clinical interventions; in such complex clinical situations as temporomandibular joint disorders, it is particularly critical to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care. Its purpose is to assist consumers, clinicians, purchasers, and policymakers to make informed decisions that will improve health care at both the individual and population levels.

In brief, perhaps the single most important use of the science of research synthesis and research meta-synthesis in the health sciences, including dentistry, head neck and oral biology, pertains to empowering the clinician to make fully informed decisions for treatments that rest not only on the patient's wants and needs, clinical tests, medical history and clinician's experience and personal awareness of the available research, but also on the best available evidence. It is important to stress the summative quality of this sine qua non: in addition to all the previous, which equate the best current clinical practice, reliance on the science of research synthesis and meta-synthesis signifies adding to the decision-making process of the best available evidence. Hence, there is the need to have reliable instruments to assess and to establish the strength of the clinical relevance and recommendations for the uncovered *best available* evidence.

Case in point, in an effort to assess the efficacy of intraoral orthotic appliances to reduce pain in patients with TMD affecting both the masticatory muscle and the joint compartment, a systematic review of clinical trials designed to compare patients who had received placebo control, no treatment, vs. other treatments was conducted. The bibliome was obtained through a stringent search strategy that included MEDLINE, the Cochrane Central Register, and manual search. Publication bias restricted the search to English language publications between January 1966 and March 2006. Inclusion/exclusion criteria included RCTs designed to assess the efficacy of hard and soft stabilization appliances, anterior positioning appliances, anterior bite appliances, and other appliance types for TMJD pain. The

[27] That is to say, statistical power even in the case of a meta-analysis performed with few papers.

main outcome measure was pain relief. CONSORT and QUORUM criteria were used to evaluate the bibliome. A total of 44 RCTs (evidence Level I) with 2218 subjects were included. Two distinct meta-analyses were conducted, as determined by homogeneity of outcomes measures: In the first meta-analysis of seven studies with 385 patients, a hard stabilization appliance was found to improve TMJD pain compared to non-occluding appliance (odds ratio (OR) = 2.46, $p = 0.001$; CI95: 1.56–3.67). In the second meta-analysis of three studies (216 patients), a hard stabilization appliance was found to improve TMJD pain compared to no-treatment controls (OR = 2.15, $p > 0.05$, CI95: 0.80–5.75). Taken together, these analyses demonstrate that hard stabilization appliances, when adjusted properly, have good evidence of effectiveness in the treatment of TMJD pain compared to non-occluding appliances and to no treatment [29].

Translational effectiveness refers to the translation of the best available evidence gathered in systematic reviews in specific clinical settings (6–9). These stringent research synthesis protocols proffer recommendations about clinical practice guideline revisions, decisions about standard of care and health information technology policy, and new research and funding directions and to fully empower patients by ensuring patient empowerment and participation through increased health literacy.

Decision-making of the best available evidence can be both qualitative and quantitative. Qualitatively, the clinical relevance of the resulting consensus of the best available diagnostic or prognostic evidence is discussed in the framework of the logic model and is described along (a) patient-centered criteria of satisfaction and quality of life, (b) practitioner satisfaction of clinical efficacy, (c) patient and clinician satisfaction about cost-effectiveness and risk-benefit ratio effectiveness, and (d) public health values and concerns, such as translation of the findings and the data into the specific clinical setting presently attending to the patient (i.e., translational effectiveness). Quantitatively, the outcomes of the research synthesis process can be utilized in a probabilistic mode of clinical decision-making that is directed to computing the probabilities of cost and risk, compared to benefits in a utilitarian model of decision-making (cf., Markovian tree). Consensus of the best available evidence will be analyzed in light of limitations of each independent systematic review and of threats to internal and external validity of the research synthesis protocol itself [9, 10].

For the purpose of dissemination of knowledge, critical summaries (i.e., "evidence reviews") of each generated systematic review are developed in a user-friendly format for the researcher, the clinician, and the policymaker, as much as the patients themselves. These summaries serve as the foundation for recommendations about each intervention reviewed to ensure that the highest-quality evidence can inform practice, policy, research, and funding decisions. These summaries also become key instruments to empower the patients by raising health literacy. Current work in our research group (cf., EBD-PBRN.org) aims at standardizing and validating the quality and value-added of evidence reviews recommendations.

One principal purpose of evidence-based revisions of clinical practice guidelines obtained from systematic reviews is to generate and analyze further directed data systematically, to address gaps in the evidence base and expansion to a global database of pathogen distribution, with the aim of improving syndrome management of TMD, prioritizing diagnostic development, and producing a guide to empirical therapy for the benefit of all stakeholders.

Despite the rapid advancement in information and communications technology over the last decade, there is limited evidence suggesting improvements in the ability of health professionals to communicate effectively. Given the critical nature of communication, it is timely and critical to initiate further evaluation of information and communication technology designed to improve communication between clinicians [30]. A framework was recently proposed by AHRQ in that respect, which was derived from a systematic patient-centered outcomes evaluation (PCOE) [9, 10] protocol that consisted of six distinct steps:

1. Focused literature review
2. Development of draft framework
3. Workshop with technical experts
4. Refinement of framework
5. Development of two case studies
6. Pilot test of framework on case studies

In brief and discussed elsewhere in greater depth [9, 10], PCOE is distinct from PCOR in that the former pursues the goal of improving existing programs, whereas the latter seeks to prove the superiority over other programs. In this process, PCOE generates new hypotheses, whereas PCOR is structured to test existing hypotheses. Both PCOE and PCOR employ the scientific process to reach the conclusions of their respective endeavors, the former obtains conclusions that are specific to the programs under evaluation, but the latter generates conclusions, which, provided the study has strong external validity, will be generalizable beyond the sample under test to the population. Researchers principally disseminate their research outcomes to their peers and fellow researchers in a constant strive to obtain a better, more precise, and more accurate understanding of fundamental mechanisms and principles. By contrast, evaluators seek to disseminate their findings to the various stakeholders who are affected, either directly or indirectly by the program under evaluation, with the primary concern of increasing cost-effectiveness of the program under evaluation or its benefit-effectiveness. That is to say, research and evaluation are two complementary aspects of the science of health care, whose interdependence is all the more timely and critical in the context of the contemporary new model of translational science in health care, in which translational research and translational effectiveness are inextricably intertwined. PCOE and PCOR are the fundamental and indispensable pillars of patient-centered, effectiveness-focused, and evidence-based health care.

The resulting framework can be characterized as having several important features combining work from a variety of fields that represent an important step forward in the rigorous assessment of such evidence because it:

- Integrates a definition of evidence based on inferential effect, not study design
- Separates evidence about the biological and physiological mechanisms from evidence derived from research synthesis aimed at linking the intervention to a given clinical outcome and evaluating efficacy and effectiveness
- Proffers the sine qua non, the essential, and the minimum sufficient set of steps for building a logic-based process based on the best evidence; is adaptable and generalizable across the health-care domains

In conclusion, this approach, developed and advocated by AHRQ for dissemination of the best evidence [31], integrates and expands previously proposed models [2, 20, 32, 33] by mirroring in the evidential framework the conceptual framework for translational medicine, thus linking the fields of basic science, evidence-based medicine, and comparative effectiveness research.

In that context, it is important to note the principal threads of intervention for TMD currently address three primary areas of work:

(a) Socioeconomic status (i.e., living conditions)
(b) Community-based (i.e., educational interventions)
(c) Biological (e.g., neuroendocrine-osteoimmunology, cf., Chiappelli [34]).
(d) Evidence-based clinical intervention.

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